PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re[illegible]ation under the Companies Act does not constitute a new legal entity but merely sub[illegible]e company to certain additional company law rules.

Signed R. Mahoney

Dated 7 November 2003

27DEC02 E773363-1 D00524
P01/7[illegible].00-0230015.0

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
23 DEC 2002
RECEIVED BY FAX

The **Patent Office**

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	**4-32832P1**	
2.	Patent application number *(The Patent Office will fill in this part)*	23 DEC 2002	0230015.0
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* 07125487005 Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND** **SWITZERLAND**	
4.	Title of invention	**Organic compounds**	
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH** **1800001**	Novartis Pharmaceuticals UK Ltd. Patents and Trademarks Wimblehurst Road HORSHAM West Sussex RH12 5AB ADP No. 07185220
6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority a[illegible] num[illegible] *(if you*
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**	

Global Phm 3/7/3

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	93
Claim(s)	9
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B. A. Yorke & Co.

Date: 23 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. J. Crook**
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

4-32832P1

DUPLICATE

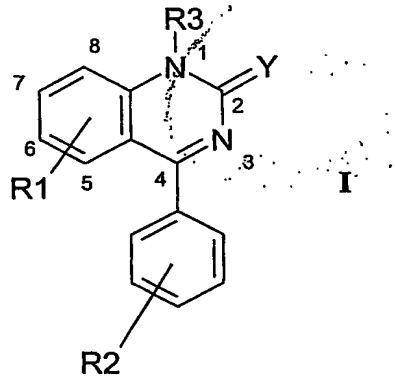
ORGANIC COMPOUNDS

This invention relates to 4-aryl-2(1H)-quinazolinone derivatives and aryl-(2-amino-phenyl)-methanone derivatives and to pharmaceutical uses thereof.

4-Aryl-2(1H)-quinazolinone derivatives and 2-substituted-4-aryl-quinazoline derivatives have been described together with their use as promoters of PTH (Parathyroid hormone) release in our copending international patent application PCT/EP 02/06606.

We have now synthesised additional new 4-aryl-2(1H)-quinazolinone derivatives and aryl-(2-amino-phenyl)-methanone derivatives which have activity as promoters of PTH release.

Accordingly the invention provides a compound of formula I



I

wherein Y is O or S;

R1 represents from 1 to 3 substituents independently selected from OH, SH, halo, NO_2, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkenyloxy, lower alkynyl, lower alkynyloxy, lower alkanoyl, lower alkylsulphone, lower alkylsulphoxide or amino);

R2 represents from 1 to 3 substituents selected from halo, optionally substituted (lower alkyl, lower alkenyl, cycloalkyl, lower alkoxy or amino);

R3 is

A) lower alkyl substituted by 1 to 3 substituents independently selected from lower alkylene, Br, F, CF_3 or $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2,

B) Benzyl which is

a. mono-or di- (preferably mono-) substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x, y and z are as defined above,

b. morpholino-lower alkoxy, aryl-lower alkoxy or optionally N-lower alkyl substituted arylamino-lower alkoxy,

c. substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy,

d. substituted on the $-CH_2-$ group thereof,

C) optionally substituted (aryl-C_2-C_8-alkyl, aryl- C_2-C_8-alkenyl, heteroarylmethyl or 4-heteroarylbenzyl); or

when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3 is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);

provided the compound of formula I is not 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-3-ylmethyl-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-2-ylmethyl-1.H.-quinazolin-2-one, 1-(6-chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-(5-nitro-furan-2-ylmethyl)-1.H.-quinazolin-2-one or 1-[2-(1.H.-indol-2-yl)-ethyl]-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-phenethyl-1H-quinazolin-2-one, 1-(2hydroxy-2-phenyl-ethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, methanesulfonic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-phenyl ester, or acetic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-yl]-1-phenyl-ethyl ester, 5-allyl-6-hydroxy-1-isopropyl-4-(4-isopropyl-phenyl)-1.H.-quinazolin-2-one;

a compound selected from 4-(4-isopropyl-phenyl)-1-(3,4-diamino-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-(2,6-dichloro-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-benzyl-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione, 1-(3di-tert-butyl-4-hydroxy-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, or 1-[3-(2-hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

Above and elsewhere in the present description the following terms have the following meanings.

Halo or halogen denote I, Br, Cl or F.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively defines such as branched or unbranched with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkyl represents; for example, methyl, ethyl, propyl, butyl, isopropyl isobutyl, or tertiary butyl.

Halo-substituted lower alkyl is C_1-C_7lower alkyl substituted by up to 6 halo atoms.

A lower alkoxy group is branched or unbranched and contains 1 to 7 carbon atoms, preferably 1-4 carbon atoms. Lower alkoxy represents for example methoxy, ethoxy, propoxy, butoxy, isopropoxy, isobutoxy or tertiary butoxy.

A lower alkene, alkenyl or alkenyloxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1-4 carbon atoms and contains at least one carbon-carbon double bond. Lower alkene lower alkenyl or lower alkenyloxy represents for example vinyl, prop-1-enyl, allyl, butenyl, isopropenyl or isobutenyl and the oxy equivalents thereof.

A lower alkyne, alkynyl or alkynyloxy group is branched or unbranched and contains 2 to 7 carbon atoms, preferably 1-4 carbon atoms and contains at least one carbon-carbon

triple bond. Lower alkyne or alkynyl represents for example ethynyl, prop-1-ynyl, propargyl, butynyl, isopropynyl or isobutynyl and the oxy equivalents thereof. (In the present description, oxygen containing substituents, e.g. alkoxy, alkenyloxy, alkynyloxy, carbonyl, etc. encompass their sulphur containing homologues, e.g. thioalkoxy, thioalkenyloxy, thioalkynyloxy, thiocarbonyl, sulphone, sulphoxide etc.)

Aryl represents carbocyclic or heterocyclic aryl.

Carbocyclic aryl represents monocyclic, bicyclic or tricyclic aryl, for example phenyl or phenyl mono-, di- or tri-substituted by one, two or three radicals selected from lower alkyl, lower alkoxy, aryl, hydroxy, halogen, cyano, trifluoromethyl, lower alkylenedioxy and oxy-C_2-C_3-alkylene; or 1- or 2-naphthyl; or 1- or 2-phenanthrenyl. Lower alkylenedioxy is a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. methylenedioxy or ethylenedioxy. Oxy-C_2-C_3-alkylene is also a divalent substituent attached to two adjacent carbon atoms of phenyl, e.g. oxyethylene or oxypropylene. An example for oxy-C_2-C_3-alkylene-phenyl is 2,3-dihydrobenzofuran-5-yl.

Preferred as carbocyclic aryl is naphthyl, phenyl or phenyl mono-, di- or trisubstituted by lower alkoxy, phenyl, halogen, lower alkyl or trifluoromethyl, especially phenyl or phenyl mono- or disubstituted by lower alkoxy, halogen or trifluoromethyl, and in particular phenyl.

Heterocyclic aryl represents monocyclic or bicyclic heteroaryl, for example pyridyl, indolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzothienyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzothiadiazolyl, furanyl, pyrrolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted as defined above.

Preferably, heterocyclic aryl is pyridyl, pyrimidyl, indolyl, quinoxalinyl, quinolinyl, benzothiadiazolyl, pyrrolyl, thiazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, imidazolyl, thienyl, or any said radical substituted, especially mono- or di-substituted as defined above.

Cycloalkyl represents a saturated cyclic hydrocarbon optionally substituted by lower alkyl which contains 3 to 10 ring carbons and is advantageously cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl optionally substituted by lower alkyl.

R1 may represent from 1 to 3 substituents; though more preferably represent 1 or 2 substituents. The R1 substituents may be present at any of positions 5, 6, 7 or 8; for instance, at positions 5, 6 or 7, e.g. when R1 represent 2 substituents these may be present at the 5 and 6 or 6 and 7 positions. Preferably one of the R1 substituents is at the 6 position.
R1 as optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkenyloxy, lower alkynyl, lower alkynyloxy, lower alkanoyl or amino) may be substituted by 1 or 2 substituents independently selected from halo, e.g. Cl, lower alkyl, e.g. ethyl or methyl, lower alkenyl, lower alkynly, cyloalkyl, e.g. C_3-C_6 cycloalkyl, or cyano.

In a particular embodiment R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), e.g. ethyl, propyl or allyl, preferably at the 5-position,

Particularly preferred significances for R1 are: propargyloxy, hydroxy, methoxy, ethoxy, allyloxy, 2-chloroethoxy, isopropoxy, n-propoxy, cyclopropylmethoxy, 3-chloropropoxy, 2-methyl-allyloxy, n-butoxy, allyl, amino, acetonitrileoxy, methylamino, dimethylamino, propargylamino, or allylamino; in particular, e.g. as hereinafter described in the Examples.

R2 represents 1, 2 or 3; for instance, 1 substituent, in the 2-position or 3-position or more preferably in the 4-position, selected from halo, optionally substituted (lower alkyl or amino) in which lower alkyl is preferably unsubstituted, e.g. branched lower alkyl, and amino is preferably mono-or di-substituted by lower alkyl.

Preferred significances for R2 include: methyl, ethyl, isopropyl, t-butyl, cyclopropyl or chloro. Most preferably R2 is isopropyl in the 4-position.

R3 as alkyl substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, may be substituted by $-SO_z$-lower alkyl, e.g. –S-lower alkyl.

R3 as Benzyl which is mono-or di- (preferably mono-) substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, may be benzyl mono-substituted by $-SO_z$-lower alkyl, e.g. $-S(O)-CH_3$ or $-S(O_2)-CH_3$.

R3 as benzyl may be substituted on the $-CH_2-$ group thereof, by 1 or 2 substituents independently selected from halogen, OH, lower alkyl, e.g. methyl, or lower alkoxy, e.g. methoxy.

R3 as optionally substituted (aryl-C_2-C_8-alkyl, aryl-C_2-C_8-alkenyl, heteroarylmethyl or 4-heteroarylbenzyl) may be substituted by up to 8, typically up to 5, usually 1, 2 or 3 substituents, independently selected from halo, nitro, cyano, amino, OH, SH, lower alkyl, lower alkoxy, lower thioalkoxy, lower alkoxycarbonyl, lower alkylsulphonyl, lower alkoxysulphonyl, lower alkylcarbonyloxy, trifluoromethyl, optionally halo-substituted aryl, optionally oxo-substituted pyrrolidinyl or –X-A-Z,

wherein

–X- is -CO-O-, –O-, $-CH_2-O-$, -CO-NR5-, -NR5-, $-CH_2-NR5-$, $-CO-CH_2-$, -S-, -S(O)-, $-S(O_2)-$, $-CH_2-S-$, $CH_2S(O)-$, $-CH_2S(O_2)-$, -SO-NR5-, $-SO_2-NR5-$, -NR5-CO-, NR5S(O)-, $NR5S(O_2)-$ or -O-CO-, where R5 is H or optionally substituted (lower alkyl, lower alkenyl, lower alkoxy-lower alkyl, aryl lower alkyl or optionally mono- or di-lower alkyl-substituted amino lower alkyl),

-A- is

C_1-C_{10} alkyl, preferably C_3-C_8 alkyl optionally interrupted by one or more, e.g. up to 4, preferably 1, 2 or 3, of –O-, -S- or –NR5-, or

HO-(lower alkoxy)$_p$-, e.g. HO(ethoxy)$_p$, or lower alkoxy-(lower alkoxy)$_p$-, e.g. methoxy-(ethoxy)$_p$, where p is an integer from 1 up to and including 10, preferably from 1 up to and including 4, and

Z is H, halo, hydroxy, lower alkoxy, lower alkoxy-lower alkoxy, -NR5R5', -N^+R5R5'R5", -COOH, imidazolyl, optionally R5 substituted -piperazinyl, -$CH(COOH)_2$, -SO_3^-, -NR5-$(CH_2)_n$-CH_2-NR5R5', -NR5-$(CH_2)_n$-CH_2-OR5, morpholino or tetrahydropyranyl,

where R5, R5' and R5" are independently H or optionally substituted (lower alkyl, lower alkoxy-lower alkyl or aryl lower alkyl, e.g. indolylethyl), or

R5, R5' or R5" may be linked together in an optionally substituted N-heterocyclic ring containing from 3 to 8 ring atoms one or more of which may comprise a further heteroatom selected from O, S or –NR5-, wherein R5 is as defined above.

R3 as optionally substituted (aryl-C_2-C_8-alkyl) may be carbocyclic aryl-C_2-C_8-alkyl, e.g. phenyl-C_2-C_8-alkyl, or hetrocyclic aryl-C_2-C_8-alkyl, e.g. pyridyl-C_2-C_8-alkyl, all optionally substituted.

R3 as optionally substituted (aryl-C_2-C_8-alkyl) may be arylethyl, aryl propyl, arylbutyl etc, e.g. phenylethyl or pyridylethyl, all optionally substituted.

R3 as optionally substituted (aryl-C_2-C_8-alkenyl) may be carbocyclic aryl-C_2-C_8-alkenyl, e.g. phenyl-C_2-C_8-alkenyl, or hetrocyclic aryl-C_2-C_8-alkenyl, e.g. pyridyl-C_2-C_8-alkenyl, all optionally substituted.

R3 as optionally substituted (aryl-C_2-C_8-alkenyl) may be arylvinyl, arylpropenyl, arylbutenyl etc, e.g. styryl or pyridylvinyl, all optionally substituted.

R3 as optionally substituted (aryl-C_2-C_8-alkyl and aryl-C_2-C_8-alkenyl) may be substituted on the aryl ring preferably by 1, 2 or 3 substituents independently selected from halogen,

nitro, cyano, amino, OH, SH, lower alkyl, lower alkoxy, lower alkyl-SO_z-$(CH_2)_y$ -O_x-, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2, or –X-A-Z, HO-(lower alkoxy)$_p$- or lower alkoxy-(lower alkoxy)$_p$ as defined above.

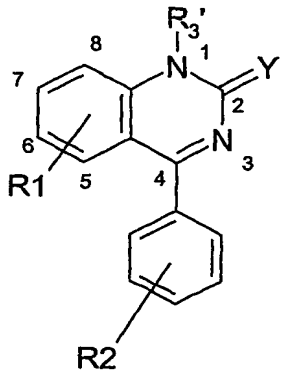
R3 as optionally substituted (aryl-C_2-C_8-alkyl and aryl-C_2-C_8-alkenyl) is optionally substituted on the C_2-C_8-alkyl or on the C_2-C_8-alkenyl by 1 to 6, preferably 1, 2 or 3 substituents independently selected from halogen, nitro, cyano, amino, OH, SH, lower alkyl, lower alkoxy, lower alkyl-SO_z-$(CH_2)_y$ -O_x-, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2, or –X-A-Z, HO-(lower alkoxy)$_p$- or lower alkoxy-(lower alkoxy)$_p$ as defined above. For example, when C_2-C_8-alkyl is ethyl, it may be substituted, e.g. at the 2-position, preferably by 1 or 2 substituents independently selected from halogen, OH, lower alkyl, e.g. methyl, or lower alkoxy, e.g. methoxy.

R3 as heteroarylmethyl is preferably pyridinylmethyl, e.g. pyridin-2-ylmethyl, pyridin-3-ylmethyl or pyridin-4-ylmethyl, imidazolylmethly, e.g. imidazol-4-ylmethyl, quinoxalinylmethyl, e.g. quinoxalin-6-ylmethyl, thiophenylmethyl, e.g. thiophen-2-ylmethyl, pyrazolylmethyl, e.g. pyrazol-3-ylmethyl, pyrimidinylmethyl, e.g. pyrimidin-5-ylmethyl, indolylmethyl, or furanylmethyl, e.g. furan-2-ylmethyl.

R3 as heteroarylmethyl is optionally substituted on the heteroaryl ring preferably by 1, 2 or 3 substituents independently selected from halogen, nitro, cyano, amino (optionally substituted by lower alkyl), OH, SH, lower alkyl (optionally substituted by halogen, nitro, amino, OH or SH), lower alkoxy, lower thioalkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, hydroxy-lower alkoxy-lower alkoxy or aryl, or –X-A-Z, HO-(lower alkoxy)$_p$- or lower alkoxy-(lower alkoxy)$_p$ as defined above..

R3 as 4-heteroarylbenzyl may comprise 4-pyrazinylbenzyl, e.g. 4-pyrazin-2-ylbenzyl, or 4-triazolylbenzyl, e.g. 4-(1,2,3)triazol-2-ylbenzyl.

Accordingly in particular embodiments the invention provides a compound of formula I'



I'

wherein Y is O or S;

R1 and R2 are as defined above for formula I;

R3' is

A) lower alkyl substituted by 1 to 3 substituents independently selected from –S-lower alkyl, lower alkylene, Br, F or CF_3,

B) benzyl which is

a. mono-or di- (preferably mono-) substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2,

b. morpholino-lower alkoxy, aryl-lower alkoxy or optionally N-lower alkyl substituted arylamino-alkoxy,

c. substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy,

C) optionally substituted (arylvinyl, arylethyl, heteroarylmethyl or 4-heteroarylbenzyl) ; or

when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3 is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);

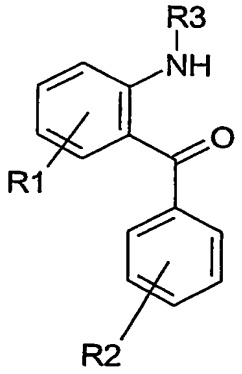
provided the compound of formula I is not 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-3-ylmethyl-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-2-

ylmethyl-1.H.-quinazolin-2-one, 1-(6-chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-(5-nitro-furan-2-ylmethyl)-1.H.-quinazolin-2-one or 1-[2-(1.H.-indol-2-yl)-ethyl]-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-phenethyl-1H-quinazolin-2-one, 1-(2hydroxy-2-phenyl-ethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, methanesulfonic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-phenyl ester, or acetic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-yl]-1-phenyl-ethyl ester, 5-allyl-6-hydroxy-1-isopropyl-4-(4-isopropyl-phenyl)-1.H.-quinazolin-2-one;

a compound selected from 4-(4-isopropyl-phenyl)-1-(3,4-diamino-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-(2,6-dichloro-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-benzyl-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione; 1-(3di-tert-butyl-4-hydroxy-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, or 1-[3-(2-hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

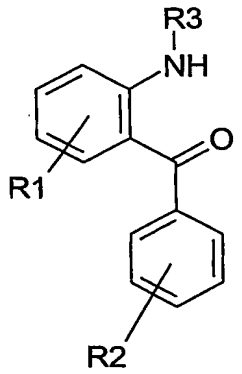
As hereinafter described compounds of formula I may be prepared by cyclisation of a compound of formula II



II

wherein R1, R2 and R3 are as defined above. Compounds of formula II have activity as promoters of PTH release and are included within the present invention, e.g. for use as PTH release promoters.

Accordingly in a further aspect the invention provides a compound of formula II



II

wherein R1, R2 and R3 are as defined above;
provided that the compound of formula II is not {2-[2-(3,5-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-3-ylmethyl)-amino]-phenyl}-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-2-ylmethyl)-amino]-phenyl}-methanone;

{2-[2-(2-hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone or {2-[(2,3-dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

Preferred significances for R1, R2 and R3 in formula II are as described above for R1, R2 and R3 in formula I.

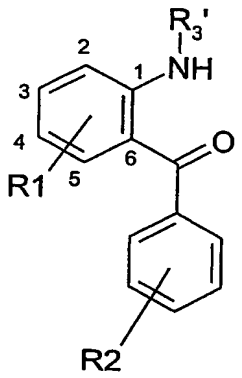
Particular signifances for R3 in formula II include:

Optionally substituted aryl-C_2-C_8-alkyl; for instance, optionally substituted phenylethyl, e.g. optionally mono-or di-lower alkoxy substituted phenylethyl, in which the ethyl is optionally mono- or di-substituted (e.g. at the 2-position) by halogen, OH, lower alkyl (e.g. methyl) or lower alkoxy (e.g. methoxy);

Optionally substituted heteroarylmethyl; for instance, optionally substituted pyridinylmethyl or quinoxalinylmethyl, e.g. optionally mono-or di-disubstituted by halogen, OH, lower alkyl (e.g. methyl), lower alkoxy (e.g. methoxy), hydroxy-lower alkoxy, (e.g. hydroxy-ethoxy) or lower alkoxy-lower alkoxy (e.g. methoxy-ethoxy); and

Benzyl which is substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy, e.g 2-(2-hydroxy-ethoxy)-benzyl.

Accordingly in particular embodiments the invention provides a compound of formula II'



II'

wherein R1 and R2 are as defined above for formula I;

R'_3 is

A) Optionally substituted aryl-C_2-C_8-alkyl;

B) Optionally substituted heteroarylmethyl; or

C) Benzyl which is substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy; or

when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3 is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);
provided that the compound of formula II' is not {2-[2-(3,5-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-3-ylmethyl)-amino]-phenyl}-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-2-ylmethyl)-amino]-phenyl}-methanone; {2-[2-(2-hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone or {2-[(2,3-dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone;
or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

The substituents and optional substituents on R3' are as described above for the optional substituents on R3, including the preferred significances thereof.

In particular the invention includes the compounds of formula I and formula II as hereinafter described in the Examples, or pharmaceutically-acceptable and –cleavable esters, or acid addition salts thereof.

The compounds of formula I and II, and salts and esters thereof, in particular as identified in the Examples are hereinafter referred to as Agents of the Invention.

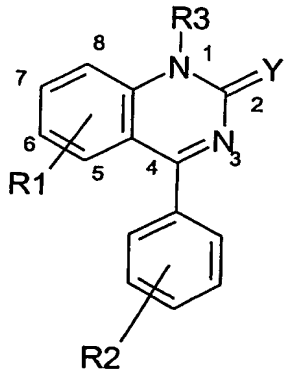
The Agents of the Invention which comprise free hydroxyl groups may also used in the form of pharmaceutically acceptable, physiologically cleavable esters, and as such and where novel are included within the scope of the invention. Such pharmaceutically acceptable esters are preferably prodrug ester derivatives, such being convertible by solvolysis or cleavage under physiological conditions to the corresponding Agents of the Invention which comprise free hydroxyl groups. Suitable pharmaceutically acceptable

prodrug esters are those derived from a carboxylic acid, a carbonic acid monoester or a carbamic acid, advantageously esters derived from an optionally substituted lower alkanoic acid or an arylcarboxylic acid.

Agents of the Invention may also exist in the form of pharmaceutically acceptable salts, and as such and where novel are included within the scope of the invention. Pharmaceutically acceptable salts include acid addition salts with conventional acids, for example, mineral acids, e.g., hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example, aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, trifluoroacetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, pamoic, methanesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example, a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

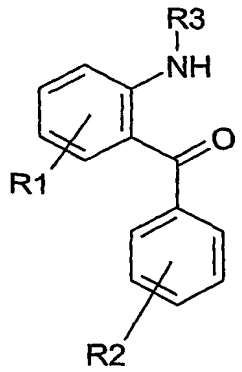
Agents of the Invention of formula I and II may be prepared as follows:

Agents of the invention of formula I



I

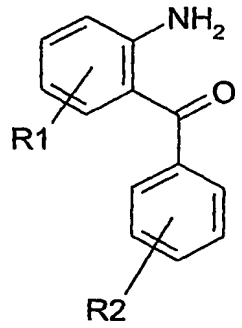
wherein R1, R2 and R3 are as defined above may be prepared by cyclising a compound of formula II



II

with a condensation reagent such as chlorosulfonyl isocyanate ($ClSO_2NCO$), sodium cyanate or sodium thiocyanate and acetic acid, and thereafter, if required converting the R1, R2 or R3 residues into an alternative R1, R2 or R3 residues to give alternative compound of formula II. For example, in the cyclisation reaction the benzophenone of formula II in solution is treated with a solution of sodium cyanate, e.g. in acetic acid at room temperature.

Benzophenone compounds of formula II may be prepared by treatment of the corresponding amine of formula X

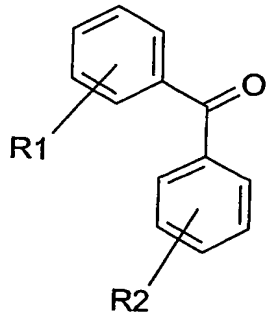


X

with the corresponding halide, e.g. bromide, R3Br and a suitable base such as K_2CO_3.

Alternatively, compounds of formula II may be prepared by reductive amination of the corresponding aldehyde with the amine X, using Ti (Oi-pr)$_4$ or molecular sieves as dehydrating agent and $NaBH(OAc)_3$ or $NaCNBH_3$ as the reducing agent. The amine X is obtainable from the corresponding nitro derivative by reduction, e.g. with Raney Nickel,

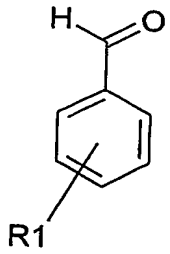
and the nitro derivative is obtainable by nitration e.g. with nitric acid, of the corresponding benzophenone of formula XI



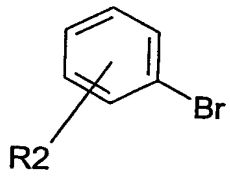
XI

wherein R2 is as previously defined and R1 is an activating group.

The compound of formula XI may in turn be obtained by the oxidation, e.g. with Jones reagent, of the corresponding alcohol which may in turn be obtained by coupling an organometallic compound derived from the corresponding bromide of formula XIII and aldehyde of formulae XII respectively; for instance as described in the Examples



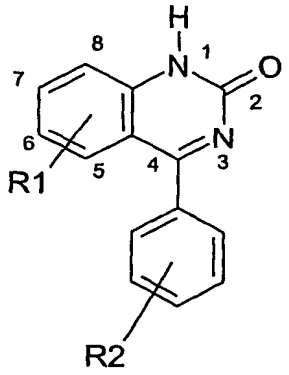
XII



XIII

In a further alternative compounds of formula II, in particular where R3 is substituted pyridyl-methyl, may be prepared by reacting the corresponding alcohol, R3-OH, e.g. pyridyl-methyl-hydroxide, with the corresponding amine of formula X, e.g. in the presence of Hünig's base and mesyl chloride; for instance as hereinafter described in the Examples.

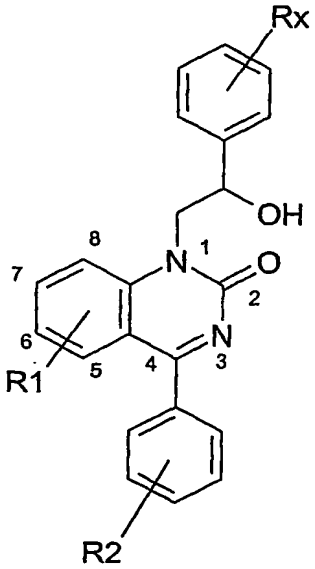
In a yet further alternative Agents of the Invention of formula II, in which R3 is optionally substituted aryl-lower alkyl may be prepared by alkylation of an Agent of the Invention of formula XX



XX

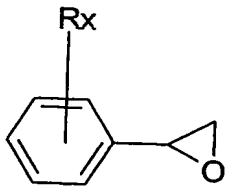
at the 1-position with the corresponding optionally substituted aryl-lower alkylhalide; for instance, in the presence of e.g. LiHMDS and NaI, in solution, e.g. THF/DMF, with mild heating.

Alternatively compounds of formula XXII



XXII

in which R3 is optionally substituted 2-phenyl-2-hydroxyethyl may be prepared by reacting a compound of formula XX with the corresponding oxirane of formula XXI



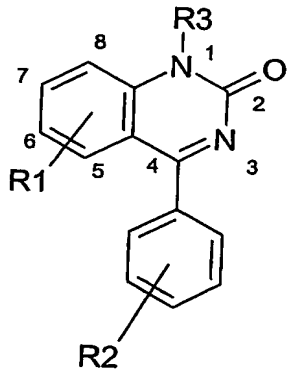
XXI

Where Rx is the optional substitution on the phenyl ring; for instance in the presence of benzyltriethylammonium chloride and potassium carbonate, e.g. as hereinafter described in the Examples. Corresponding compounds of formula II in which R3 is optionally substituted styryl may be prepared by treatment of a compound of formula XXII with a reagent such as trifluoromethanesulphonic anhydride.

The compound of formula XX may be prepared from the corresponding compound of formula II in which R3 is H by treatment with a condensation reagent such as sodium cyanate.

Agents of the Invention of formula II may be prepared as intermediates in the preparation of Agents of the Invention of formula I, e.g. as described above, or as hereinafter described in the Examples.

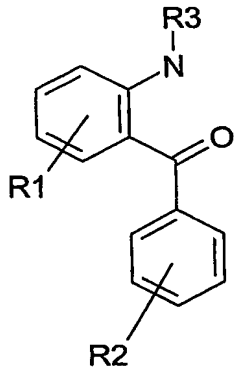
Accordingly the Invention includes processes for the preparation of Agents of the Invention of formula I



I

wherein the symbols are as defined above comprising

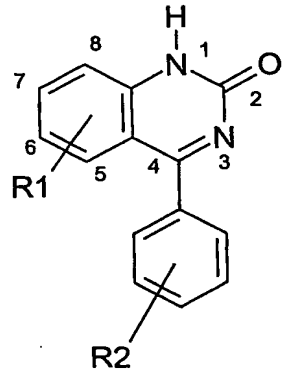
a) cyclising a compound of formula II



II

with a condensation reagent such as chlorosulfonyl isocyanate ($ClSO_2NCO$) or sodium cyanate or sodium thiocyanate; or

b) for an Agent of the Invention of formula I, in which R3 is optionally substituted aryl-lower alkyl, alkylation of a compound of formula XX

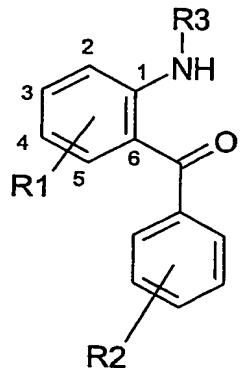


XX

at the 1-position with the corresponding optionally substituted aryl-lower alkylhalide; and thereafter, if required converting the R1, R2 or R3 residues into alternative R1, R2 or R3 residues to give an alternative compound of formula I.

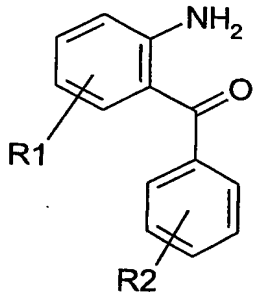
The preparation of Agents of the Invention of formula II as described above is also included within the invention.

Accordingly in a further aspect the invention provides processes for the preparation of Agents of the Invention of formula II



II

wherein R1, R2 and R3 are as defined above comprising alkylation of the corresponding aminobenzophenone compound of formula X



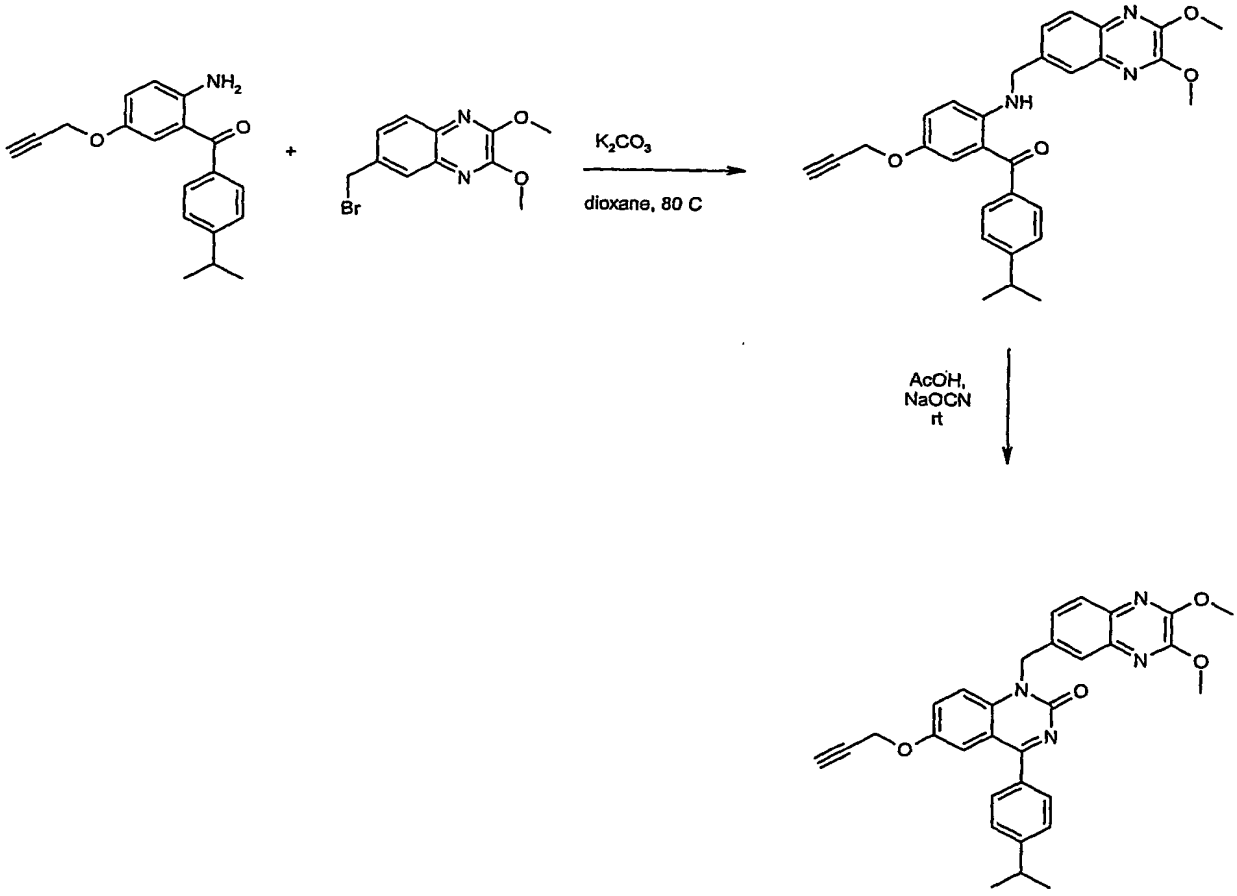
X

wherein R1 and R2 are as defined above, and thereafter, if required, converting R1, R2 or R3 residues into alternative R1, R2 or R3 residues to give an alternative compound of formula II.

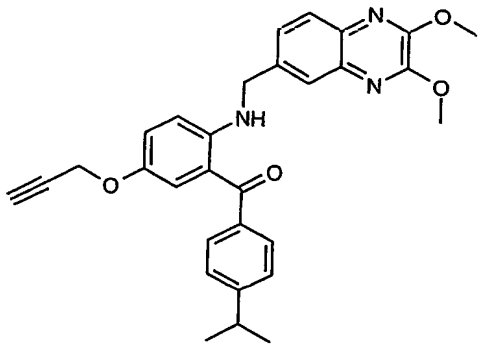
The invention is described by way of illustration only in the following non-limiting Examples which relate to the preparation of compounds of the invention of formulae I and II.

EXAMPLES

Example 1: 1-(2,3-Dimethoxy-quinoxalin-6-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



A. Synthesis of {2-[(2,3-dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone



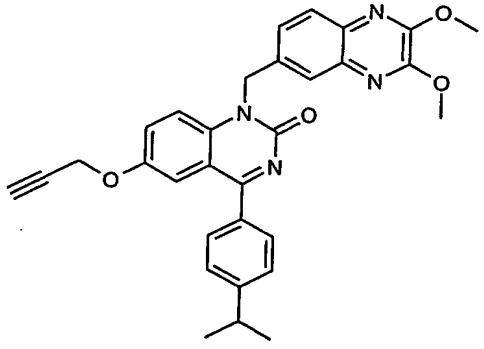
To a solution of 82 mg (0.280 mmol) (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone in 3 ml dioxane is added 193 mg (1.40 mmol) potassium carbonate and 119 mg (0.419 mmol) 6-Bromomethyl-2,3-dimethoxy-quinoxaline. The mixture is stirred at 80 °C for

two days, diluted with water and extracted with CH_2Cl_2. Purification of the crude product by chromatography (ethyl acetate/hexanes 1:1) affords 70 mg (50 %) of a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 7.04-7.60 (m, 10H), 4.94 (s, 2H), 4.52 (d, 2H), 4.26 (s, 3H), 4.08 (s, 3H), 2.96 (hept, 1H), 2.48 (t, 1H), 1.28 (d, 6H).

MS: 496 $(M+1)^+$

B. Synthesis of 1-(2,3-dimethoxy-quinoxalin-6-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



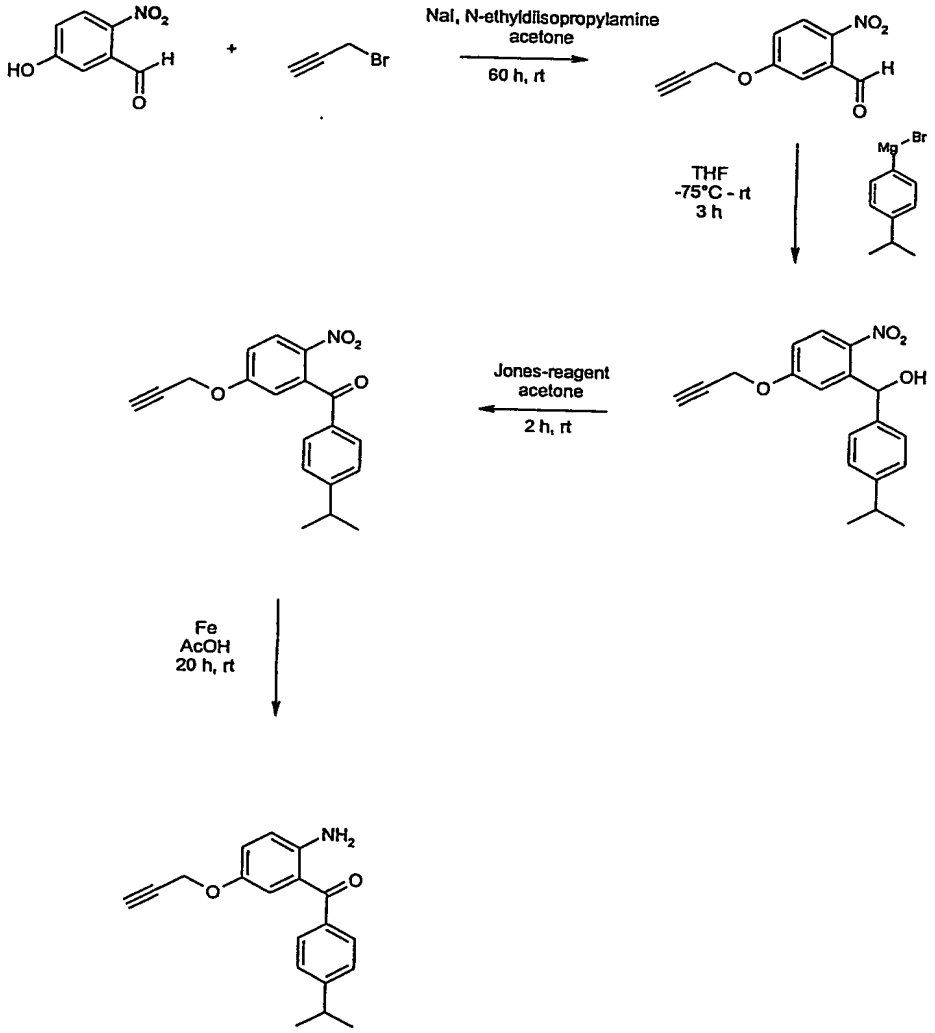
To a solution of 52 mg (0.105 mmol) {2-[(2,3-Dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone in 1 ml acetic acid is

added 14 mg (0.210 mmol) sodium cyanate. After stirring for 2 h the solvent was removed in vacuo and the residue is partitioned between CH_2Cl_2 and water. The organic layer is extracted with 2 M sodium hydroxide and evaporated. Purification of the crude product by flash-chromatography (ethyl acetate/hexanes 9:1) affords 25 mg (46%) of a yellow oil.

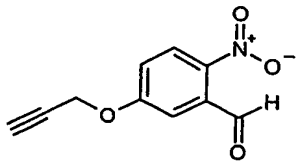
^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.70 (d, 1H), 7.48 (d, 1H), 7.14-7.51 (m, 6H), 6.10 (s, 2H),4.62 (d, 2H), 4.24 (s, 3H), 4.18 (s, 3H), 3.01 (hept, 1H), 2.52 (m, 1H), 1.32 (d, 6H).

MS: 521 $(M+1)^+$

The (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone building block is prepared as follows:



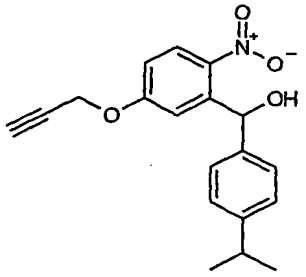
A. Synthesis of 2-nitro-5-propargyloxy-benzaldehyde



A mixture of 25 g (150 mmol) 5-hydroxy-2-nitro-benzaldehyde, 44.9 g (299 mmol) sodium iodide, 44.5 g propargyl bromide (80% in toluene), 42 ml N-ethyl-diisopropylamine and 400 ml acetone is stirred at rt for 6 d. The reaction mixture is filtered, concentrated, taken up in 1M aqueous hydrochloric acid and extracted with ethyl acetate to yield 2-nitro-5-propargyloxy-benzaldehyde.

^{1}H NMR (300 MHz, $CDCl_3$): 10.49 (s, 1H), 8.19 (d, 1H), 7.43 (s, 1H), 7.25 (d, 2H), 4.85 (s, 2H), 2.60 (s, 1H).

B. Synthesis of (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanol

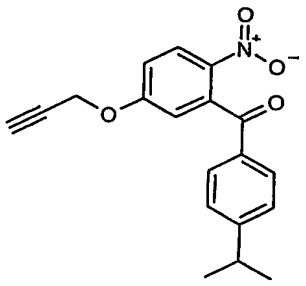


To a solution of 30.7 g (150 mmol) 2-nitro-5-propargyloxy-benzaldehyde in 200 ml THF are added at -75° during 40 min 200 ml (175 mmol) of a 0.88 M solution of 4-isopropyl magnesium bromide in THF. After stirring for 1 h at -75° saturated aqueous ammonium chloride solution is added and the reaction mixture is extracted with portions of ethyl acetate. Evaporation of the organic phases yields (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanol.

^{1}H NMR (300 MHz, $CDCl_3$): 8.09 (d, 1H), 7.45 (d, 1H), 7.26 (d, 2H), 7.19 (d, 2H), 6.98 (dd, 1H), 6.52 (broad, 1H), 4.80 (d, 2H), 2.88 (hept, 1H), 2.71 (broad, 1H), 2.56 (t, 1H), 1.23 (d, 6H).

MS: 308 (100) $(M\text{-}OH)^+$, 294 (50)

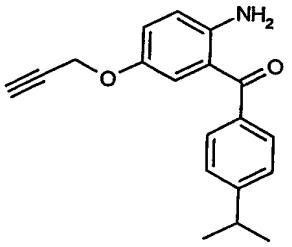
C. Synthesis of (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanone



To an ice cold solution of (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanol in 200 ml acetone are added dropwise 60 ml Jones reagent. After stirring for 2 h at rt the reaction is quenched by the addition of isopropanol and sodium bisulfite solution (40%). Extraction with dichloromethane affords (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanone.

^{1}H NMR (300 MHz, $CDCl_3$): 8.27 (d, 1H), 7.70 (d, 2H), 7.30 (d, 2H), 7.18 (dd, 1H), 6.97 (d, 1H), 4.81 (d, 2H), 2.96 (hept, 1H), 2.59 (t, 1H), 1.27 (d, 6H).

D. Synthesis of (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone

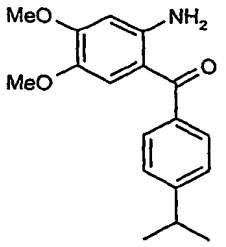


To a solution of 10.59 g (30.7 mmol) (4-isopropyl-phenyl)-(2-nitro-5-propargyloxy-phenyl)-methanone in 250 ml acetic acid are added 13.6 g (246 mmol) iron powder. After stirring for 20 h at rt the reaction mixture is basified by the addition of 2M sodium hydroxide solution, filtered and extracted with dichloromethane. After purification by chromatography using hexanes / ethyl acetate (7:3) as eluent (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone is obtained.

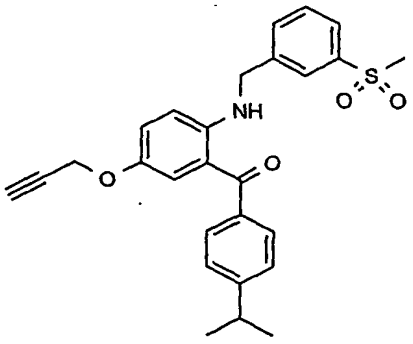
^{1}H NMR (300 MHz, $CDCl_3$): 7.64 (d, 2H), 7.30 (d, 2H), 7.12 (s, 1H), 7.05 (d, 1H), 6.72 (d, 1H), 5.71 (broad, 2H), 4.64 (s, 2H), 2.98 (hept, 1H), 2.48 (s, 1H), 1.30 (d, 6H).

MS: 294 $(M+1)^+$

The (2-amino-4,5-dimethoxy-phenyl)-(4-isopropyl-phenyl)-methanone building block is synthesised following the procedure outlined immediately above.



Example 2: 4-(4-Isopropyl-phenyl)-1-(3-methane-sulfonyl-benzyl)-5-propargyloxy - phenyl-methanone

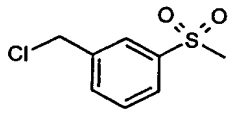


A mixture of 100 mg (0.34 mmol) (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone, 80 mg (0.58 mmol) K_2CO_3 and 77 mg (0.375 mmol)1-chloromethyl-3-methanesulphonyl-benzene in 1ml dimethylformamide was stirred at 80 °C for 6h and at 100 °C for 3 h. Then the reaction mixture was poured on water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc = 2:1) to afford 140 mg of the title compound as a yellow foam.

^{1}H-NMR (300 MHz, DMSO): 8.34 (t, 1H), 7.90 (s, 1H), 7.80 (d, 1H), 7.67 (d, 1H), 7.60-7.56 (m, 3H), 7.39 (m, 2H), 7.09 (dd, 1H), 7.01 (d, 1H), 6.70 (d, 1H), 4.61-4.53 (m, 4H), 3.54 (m, 1H), 3.19 (s, 3H), 2.96 (m, 1H), 1.25 (d, 6H).
MS: 462 $(M+1)^+$

The starting materials may be prepared as follows:

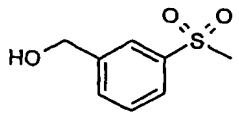
A. Synthesis of 1-chloromethyl-3-methanesulphonyl-benzene



0.267 ml (3.45 mmol) methanesulphonyl-chloride was added to o a solution of 584 mg (3.14 mmol) (3-methanesulphonyl-phenyl)-methanol and 0.6 6ml (4.71 mmol) triethylamine in 6 ml dichloromethane. This reaction mixture was stirred at room temperature for 1 h and at 50 °C for additional 3 h. The reaction mixture was then poured into water and extracted twice with dichloromethane. The combined organic layers were washed with water and brine, dried, filtered and concentrated in vacuo to afford 615 mg of the title compound, which was used in the next step without further purification.

^{1}H-NMR (300 MHz, DMSO): 7.98 (broad s, 1H), 7.86 (d, 1H), 7.77 (d, 2H), 7.64 (t, 1H), 4.86 (s, 2H), 3.21 (s, 3H).

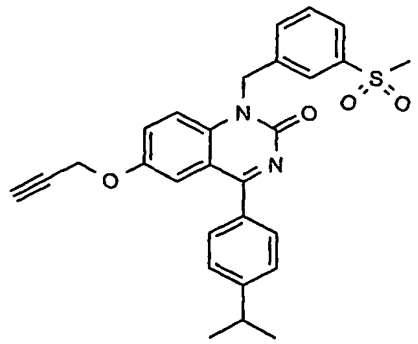
B. Synthesis of (3-Methanesulphonyl-phenyl)-methanol



$NaBH_4$ was added to a solution of 750 mg (4.08 mmol) 3-methanesulphonyl-benzaldehyde (see P.L. Ornstein, T.J. Bleisch, M.B. Arnold, R.A. Wright, B.G. Johnson, J.P. Tizzano, D.R.Helton, M.J. Kallman, D.D. Schoepp, M. Herin, *J. Med. Chem.* **1998**, *41*(3), 358-378 or B. Eistert, W. Schade, H. Selzer, *Ber.* **1964**, *97*(5), 1470-81) in 20 ml ethanol. This reaction mixture was stirred at room temperature for 1 h. After that the reaction mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried, filtered and concentrated in vacuo to afford 584 mg of the title compound, which was used in the next step without further purification.

^{1}H-NMR (300 MHz, DMSO): 7.85 (broad s, 1H), 7.78 (d, 1H), 7.62 (d, 2H), 7.59 (t, 1H), 5.45 (t, 3H), 4.58 (d, 2H), 3.19 (s, 3H).

Example 3: 4-(4-Isopropyl-phenyl)-1-(3-methane-sulfonyl-benzyl)-6-propargyloxy-1H-quinazoline-2-one.



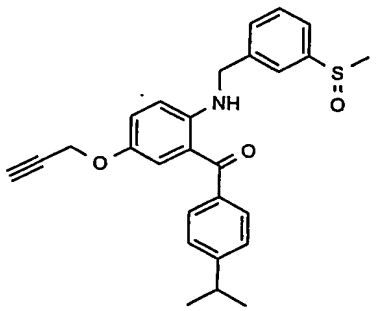
A mixture of 97 mg (0.21 mmol) 4-(4-isopropyl-phenyl)-1-(3-methane-sulfonyl-benzyl)-5-propargyloxy-phenyl-methanone and 17 mg (0.25 mmol) sodium cyanate in 3 ml acetic acid was stirred at room temperature for 72 h. Then the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash-chromatography on silica gel (hexane:EtOAc 1:3) to afford 79 mg of the title compound as a yellow foam.

^{1}H-NMR (300 MHz, DMSO): 7.95 (s, 1H), 7.81 (d, 1H), 7.70 (d, 2H), 7.61-7.50 (m, 2H), 7.47 (m, 2H), 7.45 (d, 2H), 7.38 (m, 1H), 5.59 (broad s, 2H), 4.78 (d, 2H), 3.64 (m, 1H), 3.20 (s, 3H), 3.00 (m, 1H), 1.25 (d, 6H).

MS: 487 $(M+1)^+$

The compounds of the following examples are prepared by analogy:

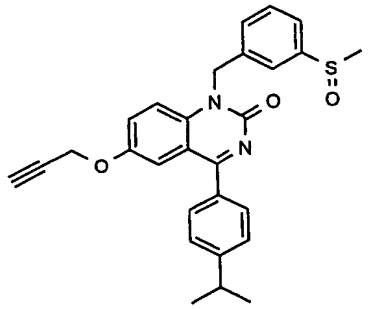
Example 4: 4-(4-Isopropyl-phenyl)-1-(3-methane-sulfonyl-benzyl)-5-propargyloxy-phenyl-methanone



The title compound can be prepared using the synthesis methodology as described using 1-chloromethyl-3-methanesulphinyl-benzene (see S.A. Laufer, G.K. Wagner *J. Med. Chem.* **2002**, *45*(13), 2733-40).

MS: 446 $(M+1)^+$

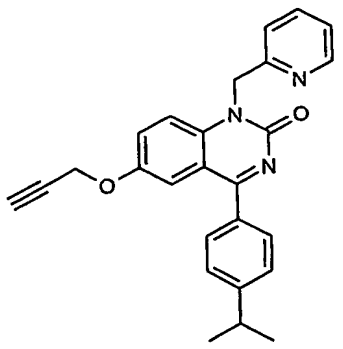
Example 5: 4-(4-Isopropyl-phenyl)-1-(3-methane-sulfinyl-benzyl)-6-propargyloxy-1H-quinazoline-2-one



^{1}H-NMR (300 MHz, DMSO): 7.70 (d, 2H), 7.66 (s, 1H), 7.58-7.44 (m, 6H), 7.39 (broad s, 1H), 7.35 (broad s, 1H), 5.59 (broad s, 2H), 4.78 (d, 2H), 3.67 (m, 1 H), 3.02 (m, 1 H), 2.72 (s, 3H), 1.28 (d, 6H).

MS: 471 $(M+1)^+$

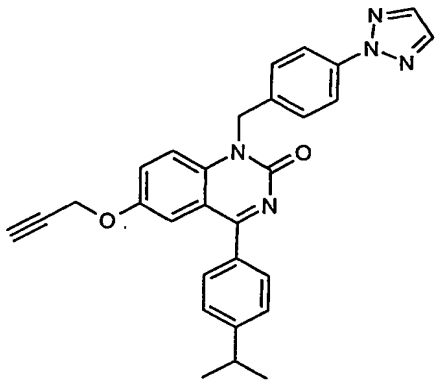
Example 6: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-pyridin-2-ylmethyl-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 8.58 (d, 1H), 7.76 (d, 2H), 7.20-7.70 (m, 8H), 5.68 (s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.54 (t, 1H), 1.32 (d, 6H).

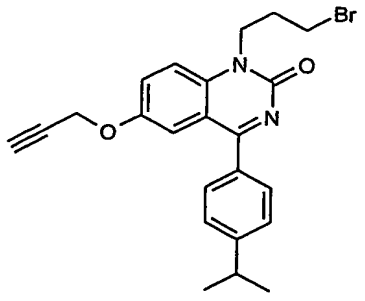
MS: 410 $(M+1)^+$

Example 7: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-(4-[1,2,3]triazol-2-yl-benzyl)-1H-quinazolin-2-one



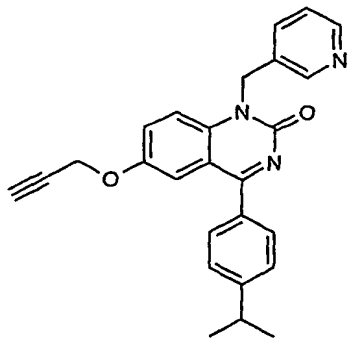
^{1}H NMR (300 MHz, $CDCl_3$): 8.04 (d, 2H), 7.72-7.80 (m, 3H), 7.20-7.52 (m, 8H), 5.60 (s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.55 (m, 1H), 1.33 (d, 6H).
MS: 476 $(M+1)^+$

Example 8: 1-(3-Bromo-propyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.69 (d, 2H), 7.46 – 7.53 (m, 3H), 7.37 (d, 2H), 4.63 (d, 2H), 4.42 (m, 2H), 3.58 (t, 2H), 2.99 (hept, 1H), 2.58 (m, 1H), 2.38 (m, 2H), 1.30 (d, 6H).
MS: 441 $(M+1)^+$

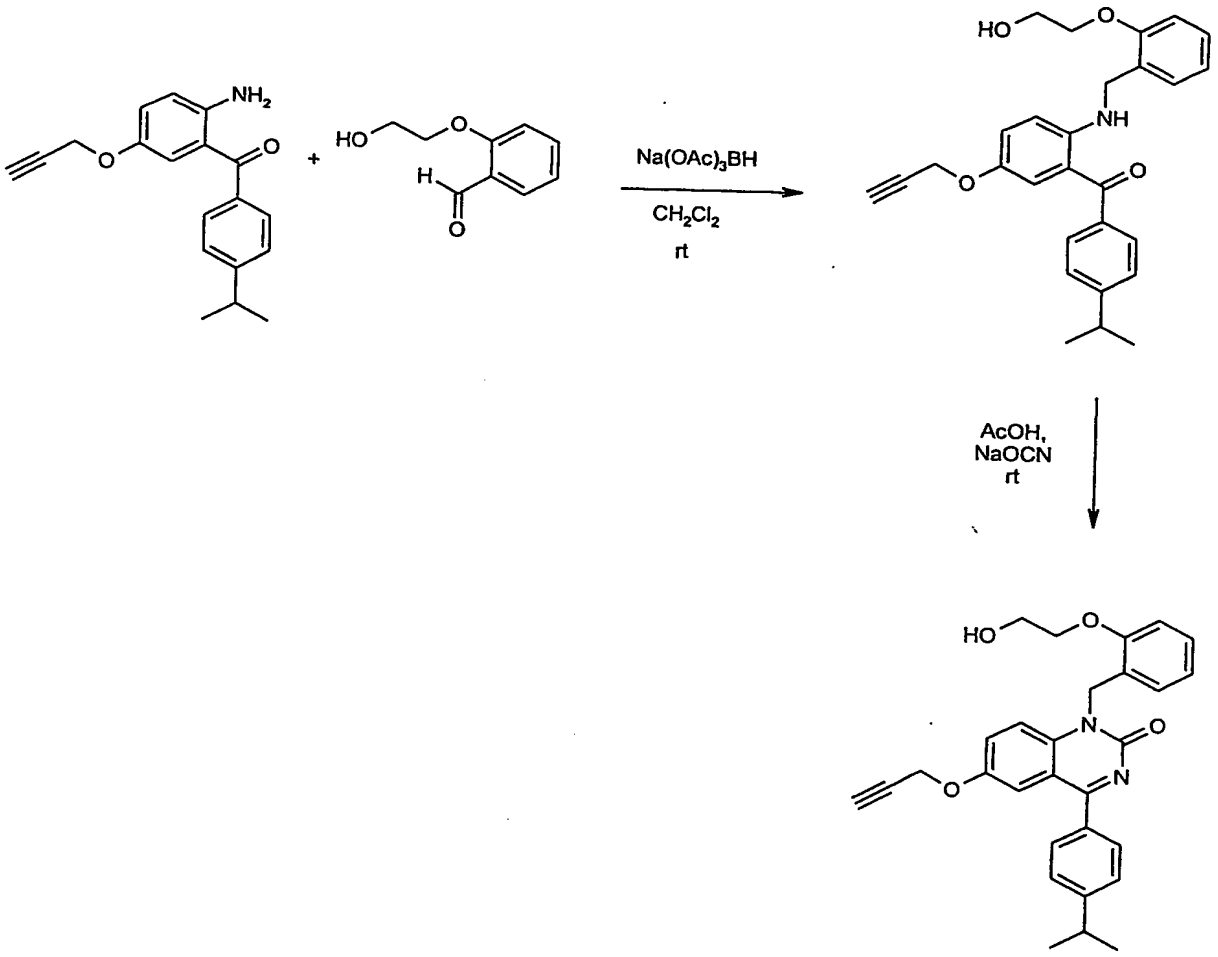
Example 9: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-pyridin-3-ylmethyl-1H-quinazolin-2-one



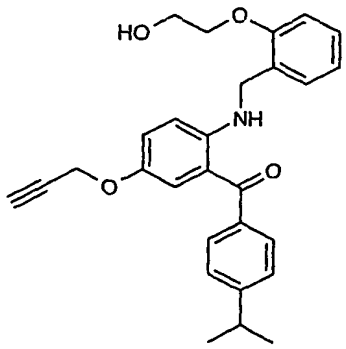
^{1}H NMR (300 MHz, $CDCl_3$): 8.78 (s, 1H), 8.58 (d, 1H), 7.90 (d, 1H), 7.74 (d, 2H), 7.54 (d, 1H), 7.26-7.44 (m, 5H), 5.60 (s, 2H), 4.64 (d, 2H), 3.01 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).

MS: 410 $(M+1)^+$

Example 10: 1-[2-(2-Hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



A. Synthesis of {2-[2-(2-Hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone

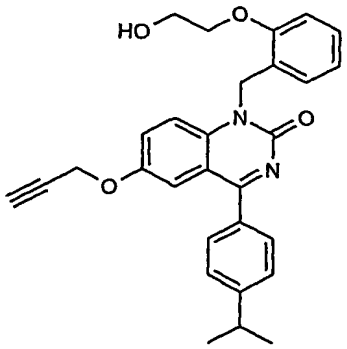


To a solution of 100 mg (0.341 mmol) (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone in 1.5 ml CH_2Cl_2 is added 61 mg (0.36 mmol) 2-(2-hydroxyethoxy)benzaldehyde and 84 mg (0.38 mmol) sodium triacetoxyborohydride. The mixture is stirred at r.t. for two days, diluted with water and extracted with CH_2Cl_2. Purification of the crude product by chromatography (ethyl acetate/hexanes 1:1) affords 115 mg (76 %) of a yellow solid.

^{1}H NMR (300 MHz, CD_3OD): 7.56 (d, 2H), 7.34 (d, 2H), 7.16-7.30 (m, 2H), 7.06-7.12 (m, 2H), 6.84-7.00 (m, 3H), 4.50-4.54 (m, 4H), 4.12 (t, 2H), 3.96 (t, 2H), 3.00 (hept, 1H), 2.92 (t, 1H), 1.32 (d, 6H).

MS: 444 $(M+1)^+$

B. Synthesis of 1-[2-(2-Hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one

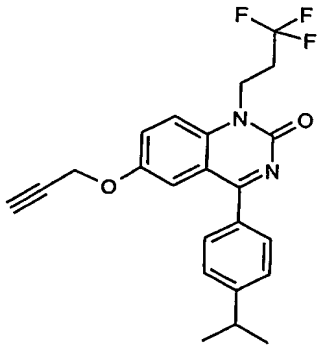


To a solution of 85 mg (0.192 mmol) {2-[2-(2-Hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone in 2 ml acetic acid is added 25 mg (0.383 mmol) sodium cyanate. After stirring for 2 h the solvent was removed in vacuo and the residue is partitioned between CH_2Cl_2 and water. The organic layer is extracted with 2 M sodium hydroxide. After evaporation of the organic phase the product is obtained as a yellow oil (85 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.20-7.56 (m, 6H), 6.94 (t, 1H), 6.86 (d, 1H), 5.62 (s, 2H), 4.04 (t, 2H), 3.94 (t, 2H), 3.02 (hept, 1H), 2.56 (m, 1H), 1.32 (d, 6H).

MS: 469 $(M+1)^+$

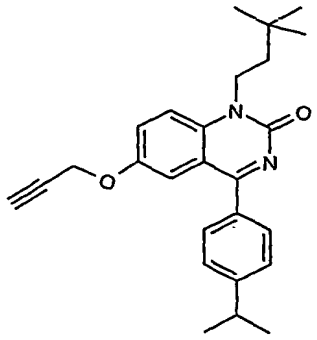
Example 11: 4-(4-Isopropyl-phenyl)-6-propargyloxy-1-(3,3,3-trifluoro-propyl)-1H-quinazolin-2-one



^{1}H-NMR (300 MHz, $CDCl_3$): 7.69 (d, 2H), 7.51 (s, 1H), 7.49 (dd, 1H), 7.37 (d, 2H), 7.33 (d, 1H), 4.68 (d, 2H), 4.47-4.56 (m, 2H), 3.01 (hept, 1H), 2.60-2.78 (m, 2H), 2.57 (t, 1H), 1.31 (d, 6H).

MS: 415 $(M+1)^+$

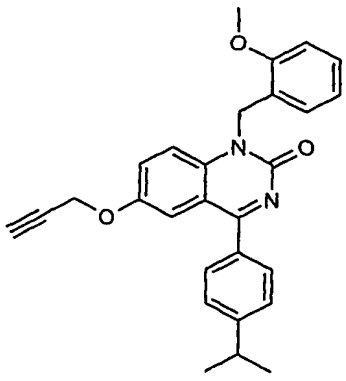
Example 12: 1-(3,3-Dimethyl-butyl)-4-(4-Isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



^{1}H-NMR (300 MHz, $CDCl_3$): 7.68 (d, 2H), 7.42-7.48 (m, 2H), 7.35 (d, 2H), 7.32 (d, 1H), 4.66 (d, 2H), 4.25-4.35 (m, 2H), 3.00 (hept, 1H), 2.56 (t, 1H), 1.66-1.74 (m, 2H), 1.31 (d, 6H), 1.10 (s, 9H). m. p. 69 °C

MS: 403 $(M+1)^+$

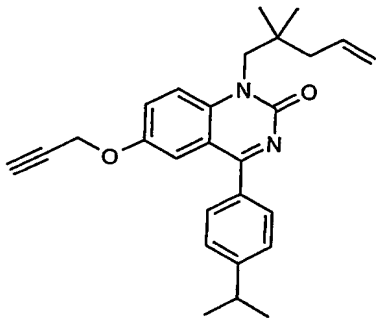
Example 13: 4-(4-Isopropyl-phenyl)-1-(2-methoxy-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.48 (d, 1H), 7.38 (d, 2H), 7.18-7.32 (m, 3H), 6.76-7.02 (m, 3H), 5.56 (s, 2H), 4.62 (d, 2H), 3.96 (s, 3H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).

MS: 439 $(M+1)^+$

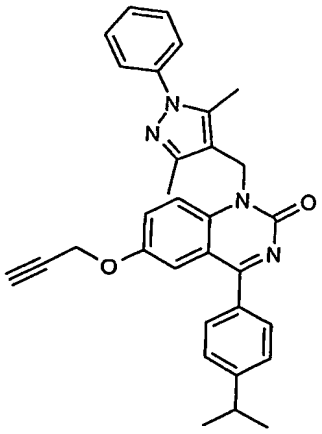
Example 14: 1-(2,2-Dimethyl-pent-4-enyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.36-7.52 (m, 5H), 5.90 (m, 1H), 5.12 (m, 2H), 4.68 (d, 2H), 4.32 (broad s, 2H), 3.02 (hept, 1H), 2.58 (m, 1H), 2.18 (d, 2H), 1.32 (d, 6H), 1.02 (s, 6H).

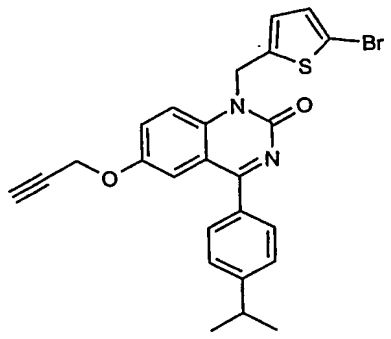
MS: 415 $(M+1)^+$

Example 15: 1-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



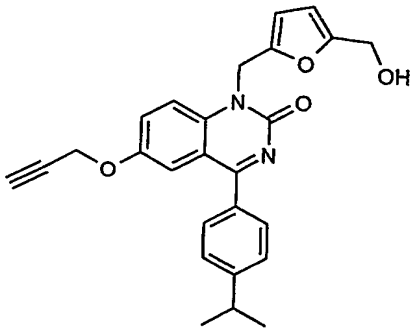
^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.52 (d, 1H), 7.26-7.50 (m, 9H), 5.48 (s, 2H), 4.66 (d, 2H), 3.02 (hept, 1H), 2.56 (m, 1H), 2.32 (s, 3H), 2.22 (s, 3H), 1.32 (d, 6H).
MS: 503 $(M+1)^+$

Example 16: 1-(5-Bromo-thiophen-2-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



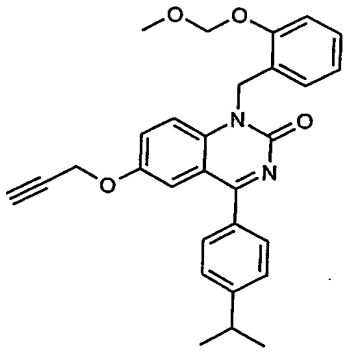
^{1}H NMR (300 MHz, $CDCl_3$): 7.68 (d, 2H), 7.31-7.50 (m, 5H), 7.34 (d, 2H), 6.94 (d, 1H), 6.88 (d, 1H), 5.52 (s, 2H), 4.64 (d, 2H), 3.00 (hept, 1H), 2.56 (m, 1H), 1.30 (d, 6H).
MS: 495 $(M+1)^+$

Example 17: 1-(5-Hydroxymethyl-furan-2-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



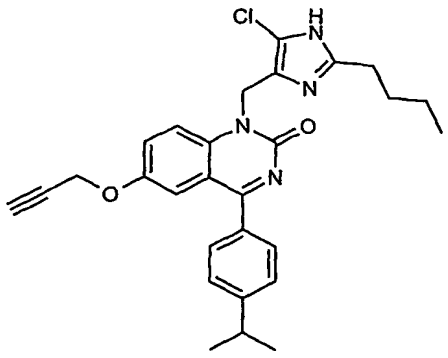
^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (d, 2H), 7.62 (d, 1H), 7.42-7.52 (m, 2H), 7.38 (d, 2H), 6.38 (d, 1H), 6.22 (d, 1H), 6.96 (dd, 1H), 5.48 (s, 2H), 4.52-4.70 (m, 4H), 3.02 (hept, 1H), 2.58 (t, 1H), 1.32 (d, 6H).
MS: 429 $(M+1)^+$

Example 18: 4-(4-Isopropyl-phenyl)-1-(2-methoxymethoxy-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



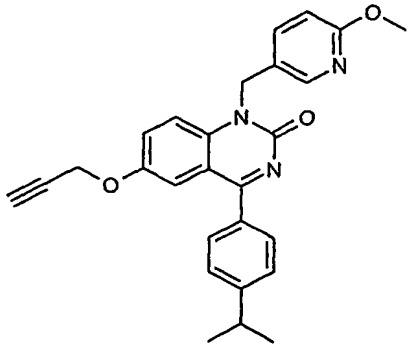
^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.48 (d, 1H), 7.38 (d, 2H), 7.10-7.32 (m, 4H), 7.02 (d, 1H), 6.86 (t, 1H), 5.58 (s, 2H), 5.34 (s, 2H), 4.62 (d, 2H), 3.58 (s, 3H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).
MS: 469 $(M+1)^+$

Example 19: 1-(2-Butyl-5-chloro-1H-imidazol-4-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, 1H), 7.46-7.60 (m, 3H), 7.38 (d, 2H), 5.36 (s, 2H), 4.66 (d, 2H), 3.00 (hept, 1H), 2.70 (m, 2H), 2.56 (t, 1H), 1.66 (m, 2H), 1.30 (d, 6H), 0.86 (t, 3H).
MS: 489 $(M+1)^+$

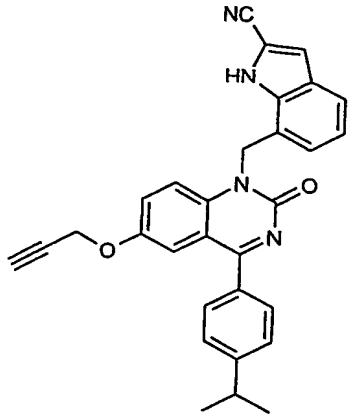
Example 20: 4-(4-Isopropyl-phenyl)-1-(6-methoxy-pyridin-3-ylmethyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 8.22 (m, 1H), 7.64-7.78 (m, 3H), 7.50 (d, 1H), 7.30-7.42 (m, 4H), 6.72 (d, 1H), 5.48 (s, 2H), 4.66 (d, 2H), 3.94 (s, 3H), 3.02 (hept, 1H), 2.56 (t 1H), 1.32 (d, 6H).

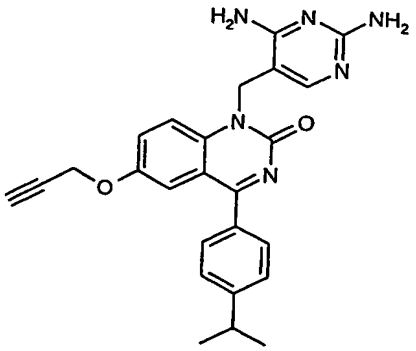
MS: 440 $(M+1)^+$

Example 21: 7-[4-(4-Isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-1H-indole-2-carbonitrile



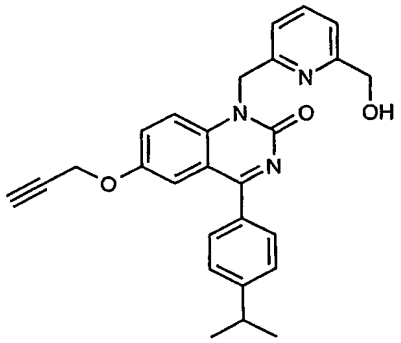
^{1}H NMR (300 MHz, $CDCl_3$): 11.52 (s, 1H), 7.92 (d, 1H), 7.74 (d, 2H), 7.64 (t, 2H), 7.46-7.54 (m, 2H), 7.38 (d, 2H), 7.12-7.26 (m, 2H), 6.76 (broad s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.56 (t 1H), 1.32 (d, 6H).
MS: 473 $(M+1)^+$

Example 22: 1-(2,4-Diamino-pyrimidin-5-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



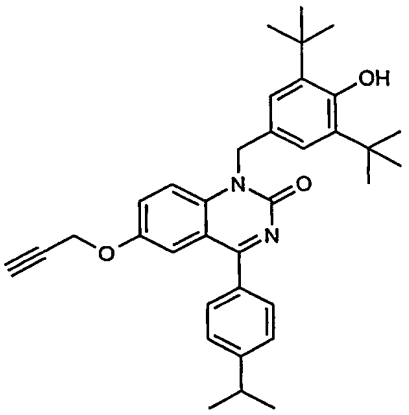
^{1}H NMR (300 MHz, CD_3OD): 7.40-7.80 (m, 8H), 5.36 (s, 2H), 4.74 (d, 2H), 2.98-3.12 (m, 2H), 1.32 (d, 6H).
MS: 441 $(M+1)^+$

Example 23: 1-(6-Hydroxymethyl-pyridin-2-ylmethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



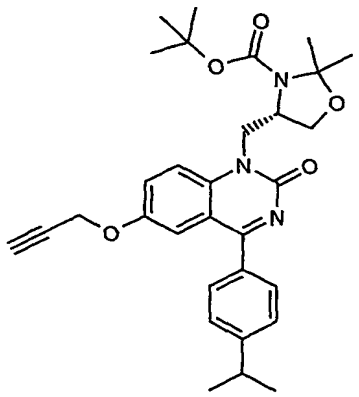
^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.64 (t, 1H), 7.20-7.52 (m, 6H), 7.16 (d, 1H), 5.64 (s, 2H), 4.76 (s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).
MS: 440 $(M+1)^+$

Example 24: 1-(3,5-Di-tert-butyl-4-hydroxy-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



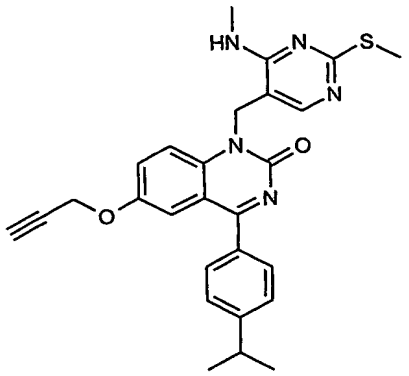
^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.30-7.52 (m, 5H), 7.16 (s, 2H), 5.44 (s, 2H), 4.66 (s, 2H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.30 (d, 6H).
MS: 537 $(M+1)^+$

Example 25: 4-[4-(4-Isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid tert-butyl ester



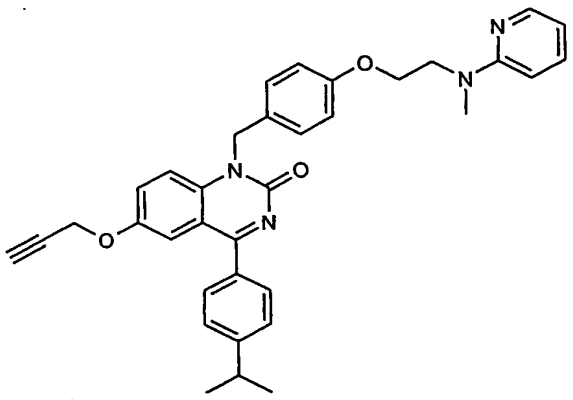
^{1}H NMR (300 MHz, $CDCl_3$): 8.20 (d, 1H), 7.70 (d, 2H), 7.30-7.58 (m, 4H), 4.94 (dd, 1H), 4.66 (d, 2H), 4.31 (d, 2H), 4.20 (m, 1H), 3.84 (dd, 1H), 3.00 (hept, 1H), 2.56 (t, 1H), 1.40-1.64 (m, 15 H), 1.32 (d, 6H).
MS: 532 $(M+1)^+$

Example 26: 4-(4-Isopropyl-phenyl)-1-(4-methylamino-2-methylsulfanyl-pyrimidin-5-ylmethyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



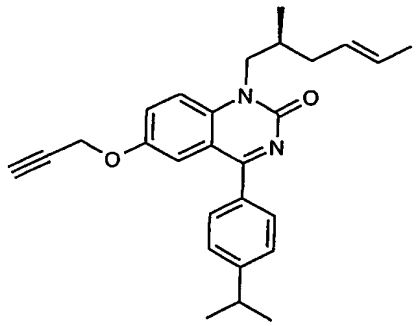
^{1}H NMR (300 MHz, $CDCl_3$): 8.18 (s, 1H), 7.86 (d, 1H), 7.72 (d, 2H), 7.64 (d, 1H), 7.52 (d, 1H), 7.44 (dd, 1H), 7.38 (d, 2H), 5.34 (broad s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.96 (d, 3H), 2.58 (t, 1H), 2.50 (s, 3H), 1.32 (d, 6H).
MS: 486 $(M+1)^+$

Example 27: 4-(4-Isopropyl-phenyl)-1-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 8.12 (dd, 1H), 7.74 (d, 2H), 7.20-7.50 (m, 7H), 6.84 (d, 2H), 6.46-6.56 (m, 2H), 5.46 (broad s, 2H), 4.64 (d, 2H), 4.36 (t, 2H), 3.92 (t, 2H), 3.12 (s, 3H), 3.02 (hept, 1H), 2.54 (t, 1H), 1.40-1.64 (m, 15 H), 1.32 (d, 6H).
MS: 559 $(M+1)^+$

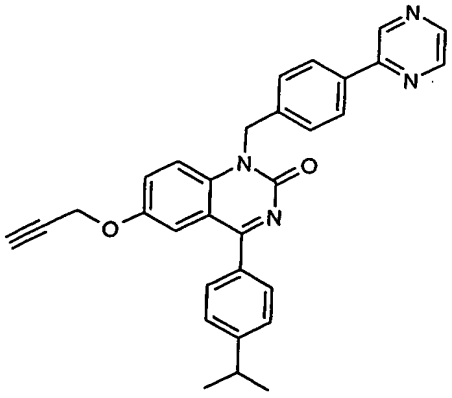
Example 28: 4-(4-Isopropyl-phenyl)-1-(2-methyl-hex-4-enyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, 2H), 7.30-7.52 (m, 5H), 5.42 (m, 2H), 4.64 (d, 2H), 4.24 (m, 2H), 3.00 (hept, 1H), 2.58 (t, 1H), 2.00-2.22 (m, 3 H), 1.62 (d, 3H), 1.30 (d, 6H), 0.98 (d, 3H).

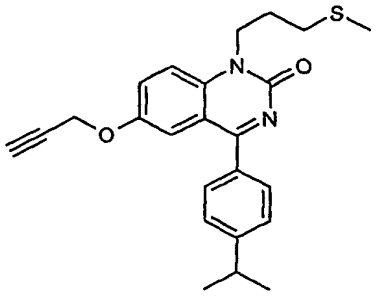
MS: 415 $(M+1)^+$

Example 29: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-(4-pyrazin-2-yl-benzyl)-1H-quinazolin-2-one



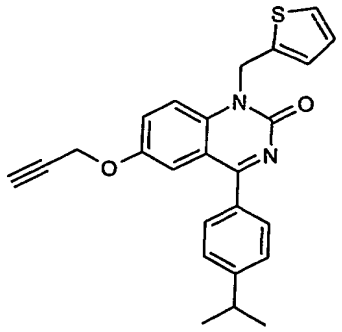
^{1}H NMR (300 MHz, $CDCl_3$): 8.88 (s, 1H), 8.60 (d, 1H), 8.46 (d, 1H), 7.88 (d, 2H), 7.76 (d, 2H), 7.20-7.58 (m, 6H), 5.62 (broad s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).
MS: 487 $(M+1)^+$

Example 30: 4-(4-Isopropyl-phenyl)-1-(3-methylsulfanyl-propyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



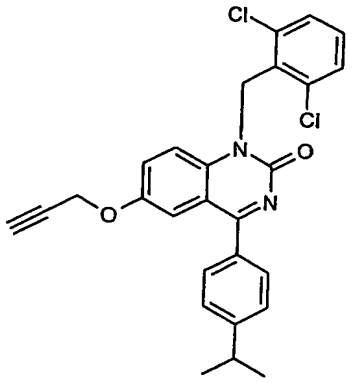
^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, 2H), 7.48 – 7.52 (m, 3H), 7.38 (d, 2H), 4.69 (d, 2H), 4.43 (dd, 2H), 3.58 (t, 2H), 3.03 (hept, 1H), 2.71 (m, 2H), 2.58 (m, 1H), 2.08-2.32 (m, 5H), 1.31 (d, 6H).
MS: 407 $(M+1)^+$

Example 31: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-thiophen-2-ylmethyl-1H-quinazolin-2-one



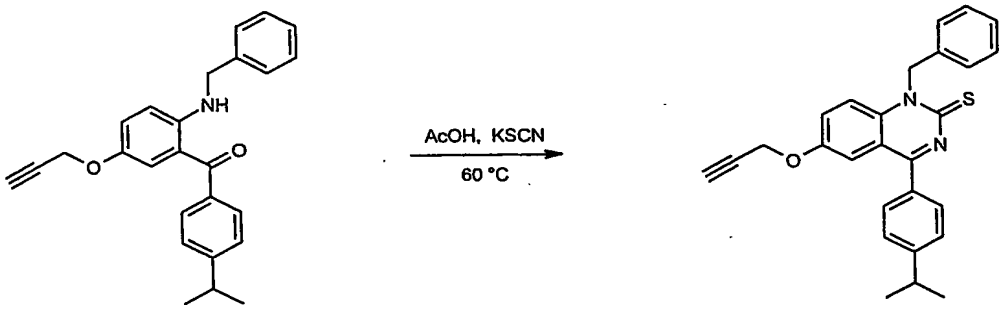
^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, 2H), 7.39-7.51 (m, 3H), 7.38 (d, 2H), 7.21 (dd, 1H), 7.18 (dd, 1H), 6.96 (dd, 1H), 5.65 (s, 2H), 4.66 (d, 2H), 3.00 (hept, 1H), 2.58 (t, 1H), 1.31 (d, 6H).
MS: 415 $(M+1)^+$

Example 32: 1-(2,6-Dichloro-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.44 (d, 1H), 7.38 (d, 2H), 7.15-7.40 (m, 5H), 5.90 (s, 2H), 4.62 (d, 2H), 3.01 (hept, 1H), 2.55 (m, 1H), 1.31 (d, 6H).
MS: 477 $(M+1)^+$

Example 33: 1-Benzyl-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione

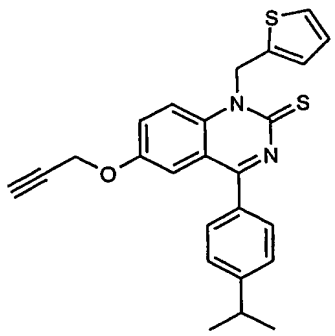


To a solution of 140 mg (0.365 mmol) (2-benzylamino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone in 5 ml acetic acid is added 68 mg (0.695 mmol) potassium thiocyanate. The reaction is stirred for two days at 60 °C. The solvent is removed and the residue is extracted with water/dichloromethane. After evaporation of the organic phase the crude product is purified by flash-chromatography ($MeOH/CH_2Cl_2$, 1:9) to give 25 mg (16%) of a yellow oil

^1H NMR (300 MHz, $CDCl_3$): 7.82 (d, 2H), 7.52 (s, 1H), 7.20–7.43 (m, 9H), 6.22 (broad s, 2H), 4.64 (d, 2H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).

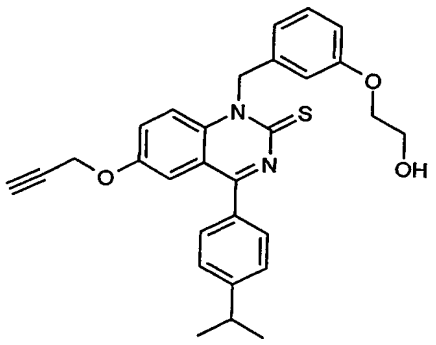
MS: 425 $(M+1)^+$

Example 34: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-thiophen-2-ylmethyl-1H quinazoline-2-thione



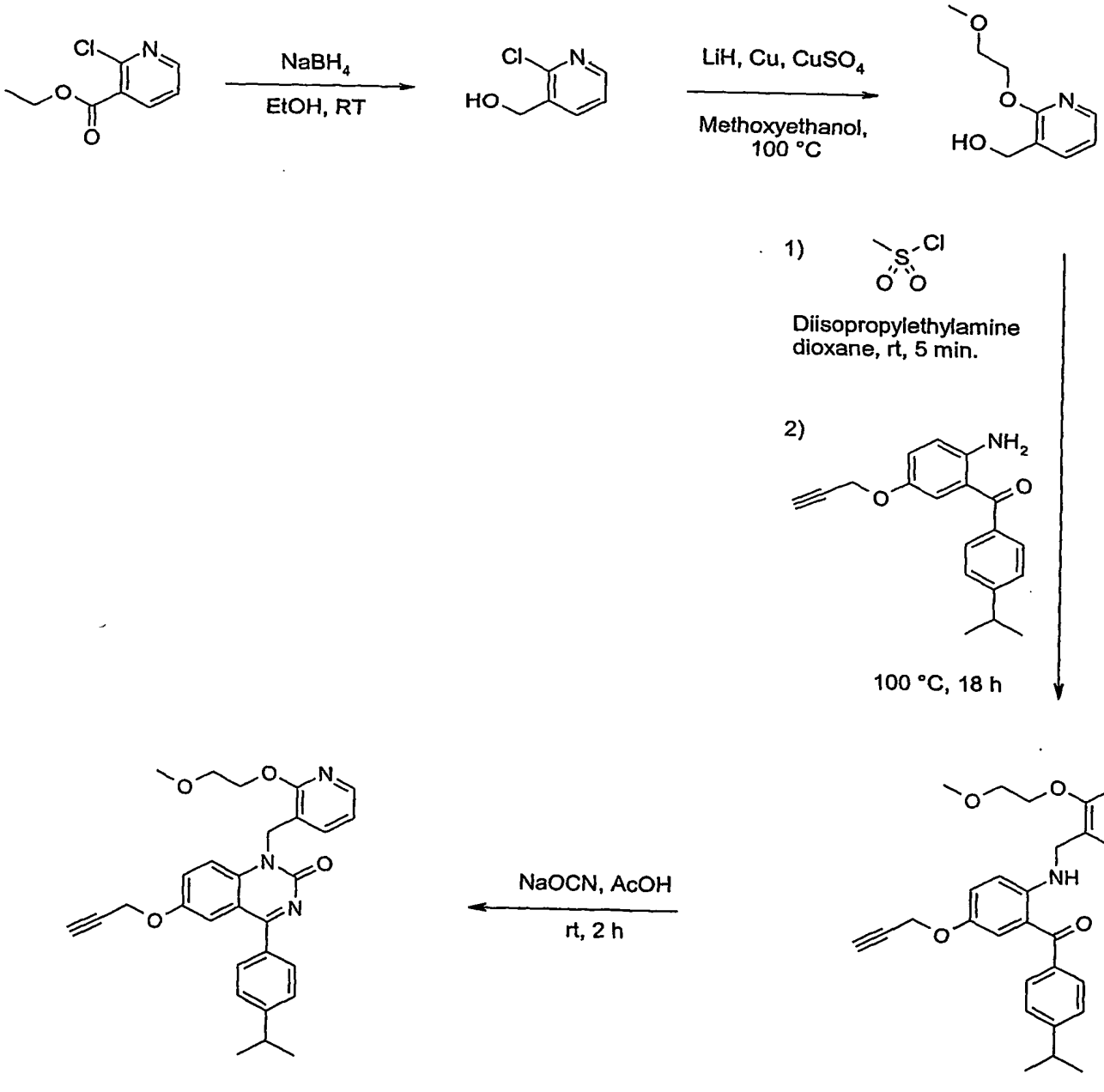
^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.64 (d, 1H), 7.50 (d, 1H), 7.44 (dd, 1H), 7.38 (d, 2H), 7.12-7.30 (m, 2H), 6.88 (m, 1H), 6.32 (broad s, 2H), 4.68 (d, 2H), 3.02 (hept, 1H), 2.58 (t, 1H), 1.32 (d, 6H).
MS: 431 $(M+1)^+$

Example 35: 1-[3-(2-Hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione

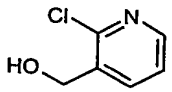


^{1}H-NMR (300 MHz, $CDCl_3$): 7.82 (d, 2H), 7.52 (m, 1H), 7.20-7.42 (m, 5H), 6.76-6.94 (m, 3H), 6.18 (broad s, 2 H), 4.66 (d, 2 H), 4.03 (t, 2H), 3.92 (t, 2H), 3.00 (hept, 1H), 2.56 (t, 1H), 1.30 (d, 6H).
MS: 485 $(M+1)^+$

Example 36: 4-(4-Isopropyl-phenyl)-1-[2-(2-methoxy-ethoxy)-pyridin-3-ylmethyl]-6-prop-2-ynyloxy-1H-quinazolin-2-one

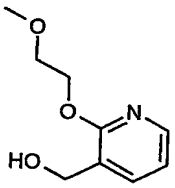


A. Synthesis of (2-chloro-pyridin-3-yl)-methanol



To a solution of ethyl 2-chloronicotinate (1g, 5.39 mmol) in 10 ml EtOH at room temperature was added 2.04 g (53.9 mmol) $NaBH_4$ over 30 minutes in several portions. The solution was stirred for. The excess borohydride was quenched with addition of methanol. The solvents were evaporated and the residue partitioned between dichloromethane and water. The aqueous Phase was extracted 3 x with 10 ml of dichloromethane. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated in vacuo to yield 690 mg (89%) of a light yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 8.42 (d, 1H), 8.04 (d, 1H), 7.40 (m, 1H), 5.41 (s, 3H) 4.82 (s, 2H).
MS: 144 $(M+1)^+$

B. Synthesis of [2-(2-methoxy-ethoxy)-pyridin-3-yl]-methanol



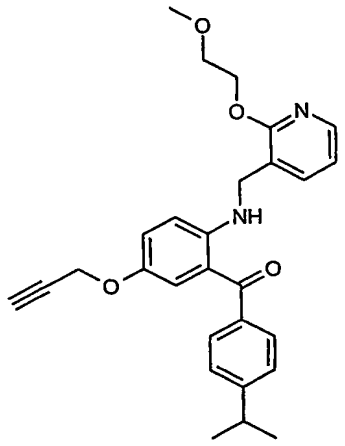
153 mg (19.2 mmol) LiH is added to 10 ml methoxyethanol and the mixture is stirred for 5 min until evolution of gas ceases. 690 mg (4.81 mmol) (2-Chloro-pyridin-3-yl)-methanol is added followed by 110 mg (1.73 mmol) Cu and 115 mg (0.721 mmol) $CuSO_4$ and the mixture is stirred at 100°C. After 2 days the reaction is cooled to r.t. and filtered with help of methanol. After evaporation ether was added to the residue and extracted

twice with brine, then dried with Na_2SO_4, filtered and evaporated until constant weight was reached.

^{1}H-NMR (300 MHz, $CDCl_3$): 8.22 (m, 1H), 7.74 (d, 1H), 7.04 (m, 1H), 5.44 (s, 3H) 4.82 (d, 2H), 4.68 (m, 2H), 3.92 (m, 2H), 3.58 (s, 3H).

MS: 184 $(M+1)^+$

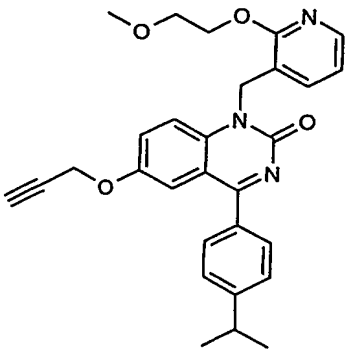
C. Synthesis of (4-isopropyl-phenyl)-(2-{[2-(2-methoxy-ethoxy)-pyridin-3-ylmethyl]-amino}-5-prop-2-ynyloxy-phenyl)-methanone



To a solution of 400 mg (2.18 mmol) [2-(2-methoxy-ethoxy)-pyridin-3-yl]-methanol in 4 ml dioxane at r.t. is added 1.12 ml (6.55 mmol) Hünig's base followed by 170 µl (2.18 mmol) mesyl chloride and the mixture was stirred for 5 min. 641 mg (2.18 mmol) (2-amino-5-propargyloxy-phenyl)-(4-isopropyl-phenyl)-methanone was added to this mixture with the addition of 1 ml of dioxane. The reaction mixture was then heated to 100°C and stirred overnight. The mixture was partitioned between ether/water and the organic layer was washed with brine, dried with Na_2SO_4, filtered and evaporated. Flash-chromatography (ethyl acetate/ether 1:1) yields 285 mg (28%) of a yellow oil

^{1}H NMR (300 MHz, $CDCl_3$): 8.04 (m, 1H), 7.56-7.64 (m, 3H), 7.30 (d, 2H), 7.20 (d, 1H), 7.08 (dd, 1H), 6.84 (dd, 1H), 6.70 (d, 1H), 4.58 (m, 2H), 4.46 (s, 2H), 3.80 (m, 2H), 3.44 (s, 3H), 2.98 (hept, 1H),1.32 (d, 6H).
MS: 459 $(M+1)^+$

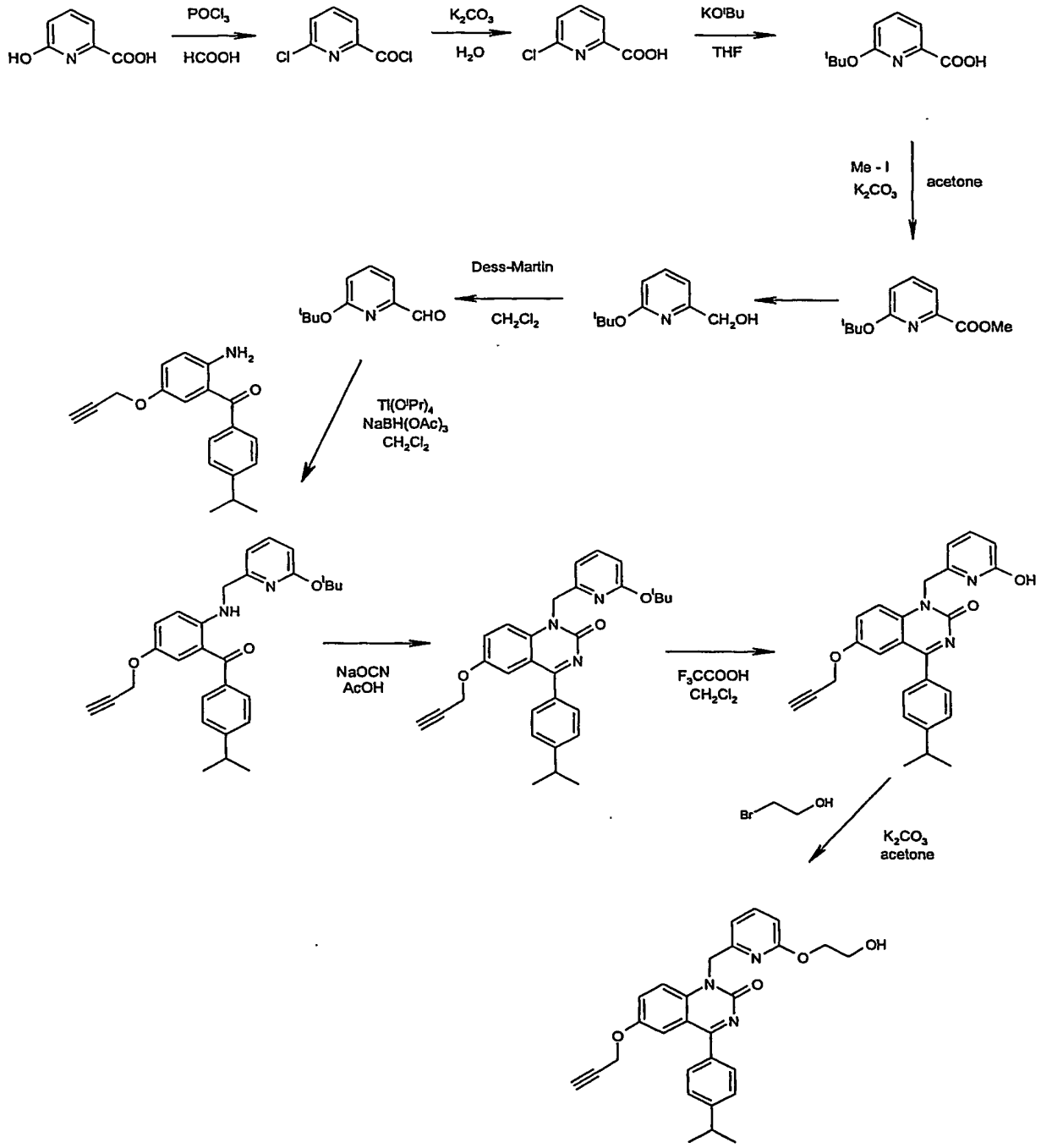
D. Synthesis of 4-(4-isopropyl-phenyl)-1-[2-(2-methoxy-ethoxy)-pyridin-3-ylmethyl]-6-prop-2-ynyloxy-1H-quinazolin-2-one



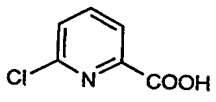
To a solution of 200 mg (0.436 mmol) (4-Isopropyl-phenyl)-(2-{[2-(2-methoxy-ethoxy)-pyridin-3-ylmethyl]-amino}-5-prop-2-ynyloxy-phenyl)-methanone in 1.5 ml acetic acid is added 28 mg (0.436 mmol) sodium cyanate. After stirring for 2 h the solvent is removed in vacuo and the residue is partitioned between CH_2Cl_2 and water. The organic layer is dried and

evaporated. Purification of the crude product by flash-chromatography (CH_2Cl_2/ether 3:7) affords 124 mg (59%) of a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$): 8.06 (d, 1H), 7.74 (d, 2H), 7.30-7.52 (m, 6H), 6.78 (dd, 1H), 5.64 (s, 2H), 4.62-4.66 (m, 4H), 3.84n(dd, 2H), 3.50 (s, 3H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.32 (d, 6H).
MS: 484 $(M+1)^+$

Example 37: Synthesis of 1-[6-(2-hydroxy-ethoxy)-pyridin-2-ylmethyl]-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



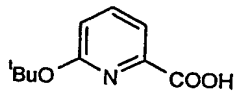
A. Synthesis of 6-chloro-pyridine-2-carboxylid acid



A suspension of 4.0 g (28.8 mmol) of 6-hydroxypicolinic acid, 6.0 ml phosphorus oxychloride and 20 g phosphorus pentachloride is slowly heated to 90 °C within 1.5 hours. Stirring is continued for another 12 h. After cooling to r.t. the mixture is quenched by careful addition of 1.4 ml formic acid. Concentration under HV affords 5.36 g of a dark solid which is subjected to hydrolysis in water (50 ml) in the presence of 5.56 g (40 mmol) potassium carbonate. Extractive work-up with petroleum ether/ water and conc. i.v. results in 2.75 g (60 %) of a slightly yellow solid. m.p. 290-183 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): 8.17 (dd, 1H), 7.93 (t, 1H), 7.62 (dd, 1H).
MS: 158 $(M+1)^+$

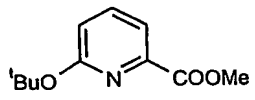
B. Synthesis of 6-tert-butoxy-pyridine-2-carboxylic acid



A solution of 2.70 g (17.1 mmol) of 6-chloro-pyridine-2-carboxylic acid in 200 ml THF is heated for 19 h to reflux. Then the mixture is poured into water and adjusted to neutral pH by the addition of citric acid. Extractive workup with ethyl acetate yields 2.67 g (80 %) of a slightly yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.72 (m, 2H), 6.94 (dd, 1H), 1.64 (s, 9H).
MS: 140 [$(M+1)^+$- butene]

C. Synthesis of 6-tert-butoxy-pyridine-2-carboxylic acid methyl ester

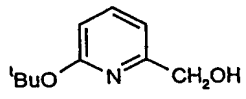


A yellow suspension of 2.60 g (13.3 mmol) of 2-tert-butoxy-pyridine-2-carboxylic acid and 2.8 g (20 mmol) potassium carbonate in 40 ml acetone is treated at r.t. with 2.64 g (18.6 mmol) of iodomethane. After stirring for 4 h at 40 °C the mixture is distributed between water and ethyl acetate. Concentration of the organic layer affords 2.32 g (83 %) of a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.58-7.64 (m, 2H), 6.81 (dd, 1H), 3.94 (s, 3H), 1.64 (s, 9H).

MS: 154 [$(M+1)^+$- butene]

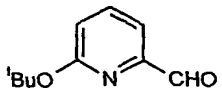
D. Synthesis of (6-tert-butoxy-pyridin-2-yl)-methanol



A solution of 2.32 g (11.1 mmol) of the ester from step C in 25 ml of ethanol is reduced by portion wise addition of 2.09 g (55. 4 mmol) of sodium borohydride. HPLC analysis after stirring at r.t. for 12 hours shows complete reaction. The mixture is diluted with methanol and extracted with ethyl acetate / water. Yield: 1.69 g (84 %) of a yellow oil.

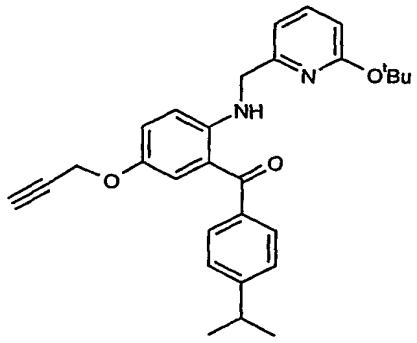
^{1}H-NMR (300 MHz, $CDCl_3$): 7.61 (dd, 1H), 6.74 (dd, 1H), 6.56 (dd, 1H), 4.65 (d, 2H), 3.42 (t, 1H), 1.60 (s,9H).

E. Synthesis of 6-tert-butoxy-pyridin-2-carbaldehyde



1.65 g (9.10 mmol) of the alcohol obtained in step D in 50 ml dichloromethane is oxidised with 3.86 g (9.10 mmol) of Dess-Martin periodinane. The reaction is complete after 12 h. The reaction mixture is extracted with ethyl acetate / aqueous sodium thiosulfate solution and the organic layer concentrated i.V. Flash-chromatography of the crude product (petroleum ether / ethyl acetate) affords 1.21 g (74 %) of a yellow oil.
^{1}H-NMR (300 MHz, $CDCl_3$): 9.91 (s, 1H), 7.67 (t, 1H), 7.50 (dd, 1H), 6.86 (dd, 1H), 1.66 (s, 9H).
MS: 124 [$(M+1)^+$- butene]

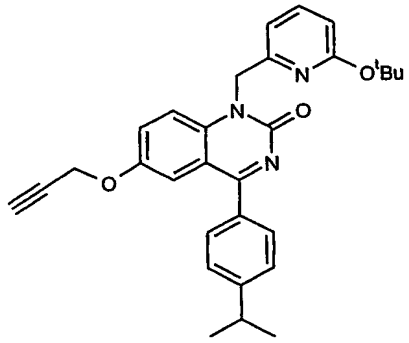
F. Synthesis of {2-[(6-tert-butoxy-pyridin-2-ylmethyl)-amino]-5-propargyloxy-phenyl}-(4-isopropyl-phenyl)-methanone



A solution of 600 mg (2.05 mmol) of (2-amino-5-propargyloxy-phenyl)-4-isopropyl-phenyl)-methanone and 403 mg (2.25 mmol) of the aldehyde obtained in the step above in 18 ml dichloromethane is treated with 872 mg (3.07 mmol) of titanium(IV)isopropoxyde. The imine obtained after stirring overnight is reduced with 650 mg (3.07 mmol) of sodium triacetoxyborohydride in the presence of 2.4 ml of EtOH. The crude product after extractive workup with ethyl acetate / petroleum ether is purified by flash chromatography (ethyl acetate / petroleum ether). Yield: 445 mg (47 %) of a yellow oil.

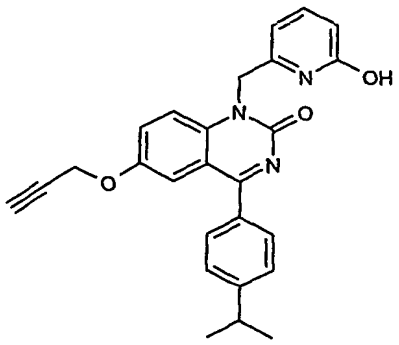
^{1}H-NMR (300 MHz, $CDCl_3$): 7.61 (d, 2H), 7.46 (dd, 1H), 7.30 (d, 2H), 7.21 (d, 1H), 7.04-7.11 (m, 1H), 6.86 (d, 1H), 6.72 (d, 1H), 6.63 (d, 1H), 4.53 (d, 2H), 4.48 (d, 2H), 2.99 (hept, 1H), 2.48 (t, 1H), 1.60 (s, 9H), 1.34 (d, 6H).
MS: 457 $(M+1)^+$

G. Synthesis of 1-[(6-tert-butoxy-pyridin-2-ylmethyl)-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



A solution of 120 mg (0.26 mmol) of the starting material (step F) in 3 ml acetic acid is cyclised with 21 mg (0.315 mmol) sodium cyanate overnight to afford 95 mg (75 %) of the quinazolinone after flash-chromatography (hexane / ethyl acetate). m.p. 62-65 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): 7.72 (d, 2H), 7.46-7.50 (m, 2H), 7.43 (d, 1H), 7.39 (d, 2H), 7.31 (dd, 1H), 6.90 (d, 1H), 6.52 (d, 1H), 5.56 (broad s, 2H), 3.03 (hept, 1H), 2.55 (t, 1H), 1.41 (s, 9H), 1.33 (d, 6H).
MS: 482 $(M+1)^+$

H. Synthesis of 1-[(6-tert-pyridin-2-ylmethyl)-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one

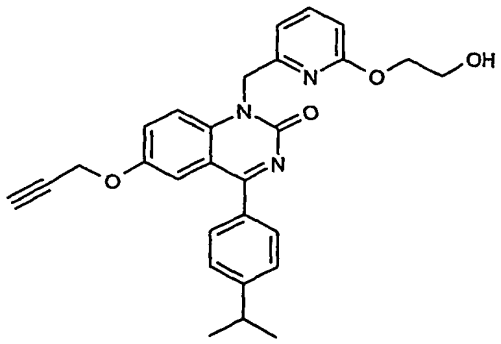


A mixture of 60 mg (0.13 mmol) of the t-butyl ether (step G) in 6 ml dichloromethane is treated with 15 µl trifluoroacetic acid and stirred overnight at rt. Extractive workup with aqueous sodium bicarbonate solution / dichloromethane yields 38 mg (69 %) of a yellow solid. m.p. 219-222 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.55 (d, 1H), 7.32-7.48 (m, 5H), 6.50 (d, 1H), 6.23 (d, 1H), 5.38 (broad s, 2H), 4.69 (d, 2H), 3.04 (hept, 1H), 2.58 (t, 1H), 1.34 (d, 6H).

MS: 426 $(M+1)^+$

I. Synthesis of Synthesis of 1-[6-(2-hydroxy-ethoxy)-pyridin-2-ylmethyl]-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



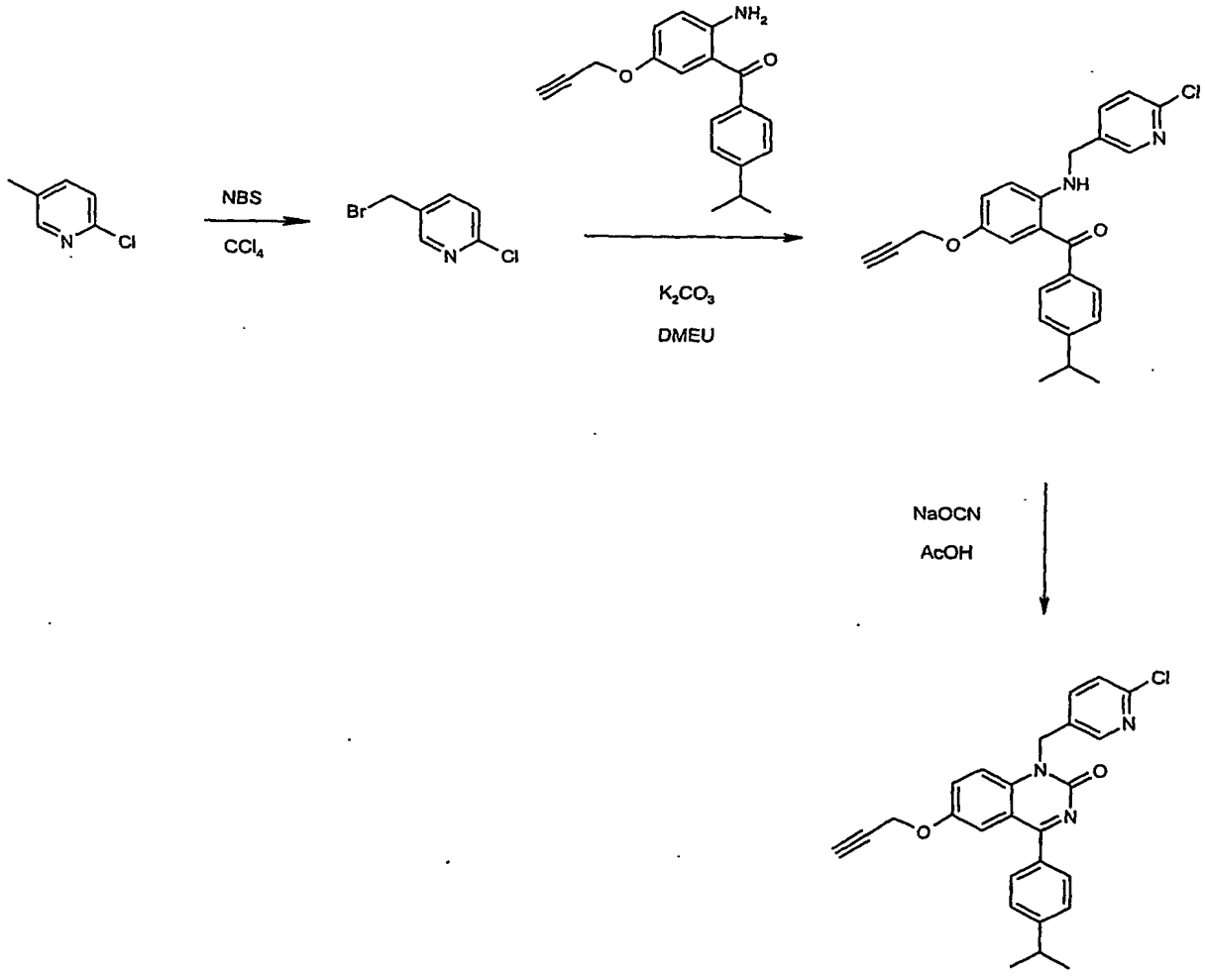
A suspension of 40 mg (0.094 mmol) of the pyridyl-alcohol obtained in step H, 16 mg (0.132 mmol) 2-bromoethanol and 19 mg (0.141 mmol) potassium carbonate in 4 ml acetone is stirred overnight at 70 °C. The crude product obtained after extraction with

ethyl acetate /water is purified by flash chromatography (hexane / ethyl acetate) to yield 32 mg (72 %) of a yellow oil.

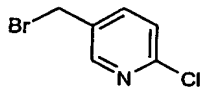
^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (d, 2H), 7.32-7.56 (m, 6H), 6.92 (d, 1H), 6.68 (d, 1H), 5.53 (broad s, 2H), 4.66 (d, 2H), 4.38-4.52 (m, 2H), 3.91 (broad, 2H), 3.02 (hept, 1H), 2.75 (broad, OH), 2.56 (t, 1H), 1.33 (d, 6H).

MS: 470 $(M+1)^+$

Example 38: 1-[6-Chloro-pyridin-3-ylmethyl]-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



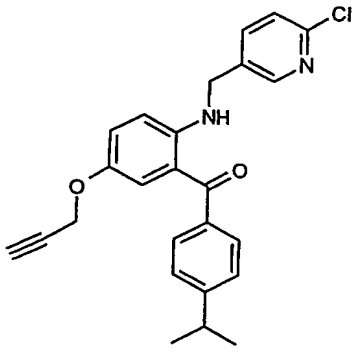
A. Synthesis of 2-bromomethyl-2-chloro-pyridine



A solution of 1.28 g (10.0 mmol) 2-chloro-5-methyl-pyridine in 25 ml carbon tetrachloride is treated with 1.79 g (10.0 mmol) of freshly recrystallised N-bromosuccinimid and 30 mg benzoyl peroxide. The mixture is heated to reflux for 17 h and filtered. The filtrate is washed with water and concentrated. Flash chromatography (hexane / ethyl acetate) results in 750 mg (36 %) of a white low melting solid. m.p. 40-43 °C.

MS: 210 (2), 208 (100), 206 (75) (chloro-bromo isotope pattern) $(M+1)^+$

B. Synthesis of {2-[(6-chloro-pyridin-3-ylmethyl)-amino]-5-propargyloxy-phenyl}-(4-isopropyl-phenyl)-methanone



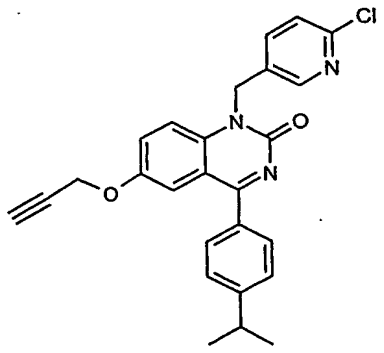
To a solution of 323 mg (1.10 mmol) of (2-amino-5-propargyloxy-phenyl)-4-isopropyl-phenyl)-methanone and 250 mg (1.21 mmol) of 2-bromomethyl-2-chloro-pyridine (step A) in 2 ml 1,3-dimethyl-2-imidazolidinone (DMEU) 213 mg (1.54 mmol) of potassium carbonate are added. The reaction is complete after stirring for 2 h at 60 °C. The cooled

yellow suspension is distributed between ethyl acetate and bicarbonate solution. Flash chromatography (hexane / ethyl acetate) affords 350 mg (76 %) of a yellow solid. m.p. 96 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): 8.49 (t, 1H), 8.40 (d, 1H), 7.67 (dd, 1H), 7.61 (d, 2H), 7.31 (d, 2H), 7.30 (d, 1H), 7.23 (d, 1H), 7.08 (dd, 1H), 6.59 (d, 1H), 4.53 (d, 2H), 4.48 (d, 2H), 2.99 (hept, 1H), 2.48 (t, 1H), 1.31 (d, 6H).

MS: 419 $(M+1)^+$

C. Synthesis of 1-[(6-chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one

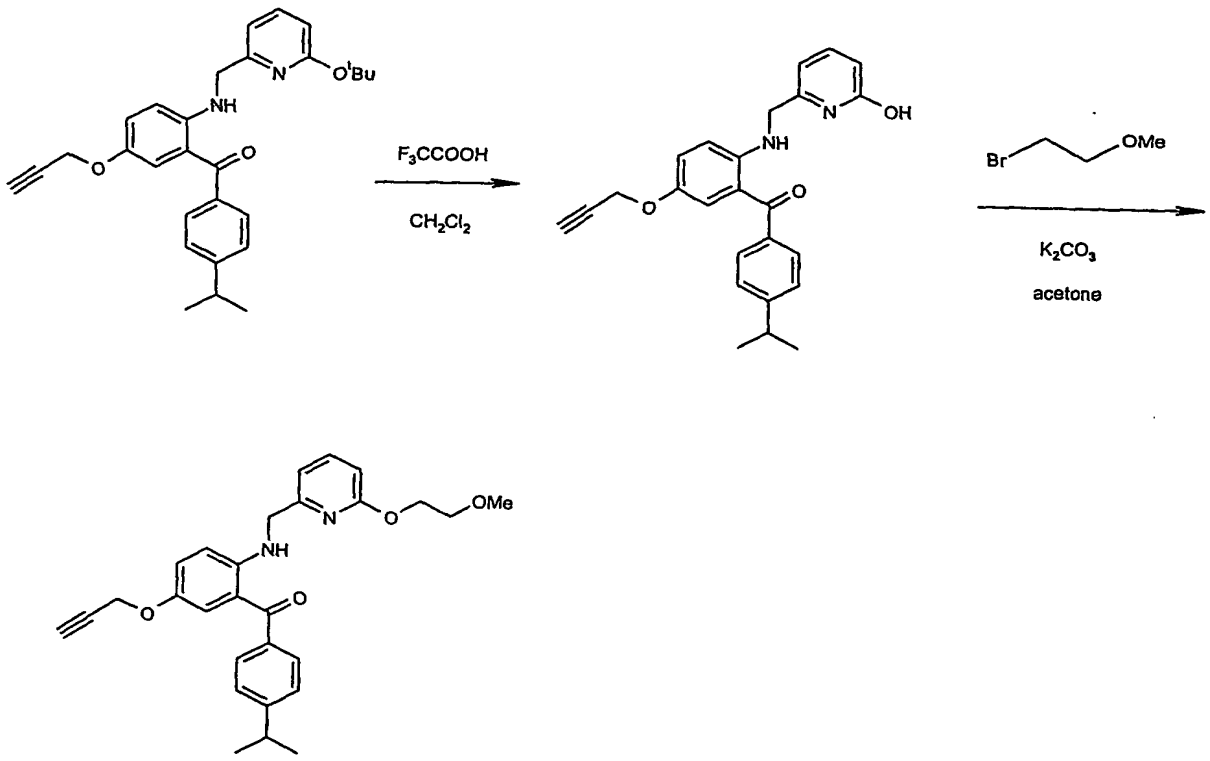


A solution of 320 mg (0.764 mmol) of the starting material (step B) in 4 ml acetic acid is cyclised with 74 mg (1.15 mmol) sodium cyanate. A thick suspension results after 3 h. Distribution between ethyl acetate and aqueous bicarbonate solution, concentration of the organic layer and flash chromatography (hexane / ethyl acetate) of the crude product yields 87 mg (26 %) of the title quinazolinone in the form of a yellow solid. m.p. 210 °C.

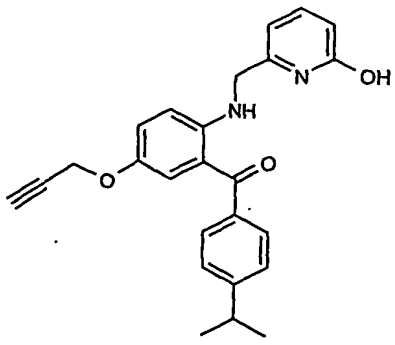
^{1}H-NMR (300 MHz, $CDCl_3$): 8.44 (d, 1H), 7.72 (d, 2H), 7.67 (dd, 1H), 7.61 (d, 1H), 7.38 (d, 2H), 7.36 (dd, 1H), 7.27 (d, 1H), 7.21 (d, 1H), 5.51 (broad, 2H), 4.65 (d, 2H), 3.01 (hept, 1H), 2.55 (t, 1H), 1.31 (d, 6H).

MS: 444 $(M+1)^+$

Example 39: (4-Isopropy-phenyl)-(2-{[6-(2-methoxy-ethoxy)-pyridin-2-ylmethyl]-amino}-5-propargyloxy-phenyl)-methanone



A. Synthesis of {2-[(6-hydroxy-pyridin-3-ylmethyl)-amino]-5-propargyloxy-phenyl}-(4-isopropyl-phenyl)-methanone

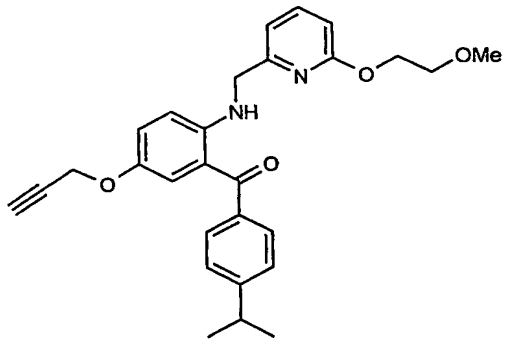


A solution of 120 mg (0.263 mmol) of {2-[(6-tert-butoxy-pyridin-2-ylmethyl)-amino]-5-propargyloxy-phenyl}-(4-isopropyl-phenyl)-methanone (Example 37, step F) in 3 ml dichloromethane is treated with 30 µl trifluoroacetic acid and stirred overnight. Workup with ethyl acetate and aqueous bicarbonate solution and flash chromatography of the crude product results in 77 mg (73 %) of a yellow solid. m.p. 189-193 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): 7.65 (d, 2H), 7.40 (dd, 1H), 7.33 (d, 2H), 7.24 (d, 1H), 7.08 (dd, 1H), 6.58 (d, 1H), 6.45 (d, 1H), 6.24 (d, 1H), 4.55 (d, 2H), 4.40 (d, 2H), 3.01 (hept, 1H, 2.49 (t, 1H), 1.32 (d, 6H).

MS: 401 $(M+1)^+$

B. Synthesis of Synthesis of (4-isopropy-phenyl)-(2-{[6-(2-methoxy-ethoxy)-pyridin-2-ylmethyl]-amino}-5-propargyloxy-phenyl)-methanone

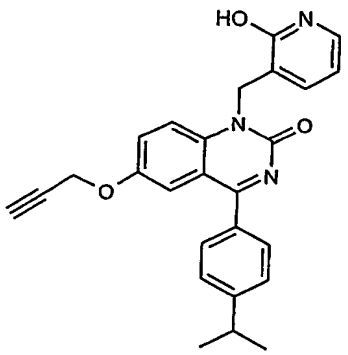


A suspension of 50 mg (0.125 mmol) of the pyridyl-alcohol obtained in step A, 13 µl (0.137 mmol) 2-bromoethyl methyl ether and 26 mg (0.187 mmol) potassium carbonate in 6 ml acetone is stirred overnight at 70 °C. The crude product obtained after extraction with ethyl acetate / water is purified by flash chromatography (hexane / ethyl acetate) to yield 20 mg (35 %) of yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): 8.83 (t, NH), 7.62 (d, 2H), 7.52 (dd, 1H), 7.30 (d, 2H), 7.21 (d, 1H), 7.10 (dd, 1H), 6.90 (d, 1H), 6.69 (dd, 2H), 4.60 (dd, 2H), 4.53 (d, 2H), 4.48 (d, 2H), 3.78(dd, 2H), 3.44 (s, 3H), 2.99 (hept, 1H), 2.48 (t, 1H), 1.31 (d, 6H).

MS: 459 $(M+1)^+$

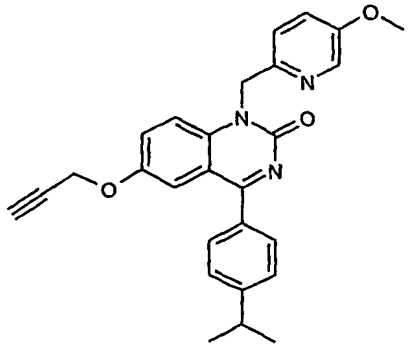
Example 40: 1- (2-Hydroxy-pyridin-3-ylmethyl)-4-(4-isopropy-phenyl)-6-propargyloxy-1H-quinazolin-2-one



A solution of 290 mg (0.635 mmol) of {2-[(2-tert-butoxy-pyridin-3-ylmethyl)-amino]-5-propargyloxy-pheny}-(4-isopropyl-phenyl)-methanone and in 7 ml acetic acid is reacted with 50 mg (0.762 mmol) sodium cyanate. After stirring overnight the mixture is distributed between ethyl acetate and aqueous bicarbonate solution. The organic layer is concentrated to yield 240 mg (88 %) of the title compound in the form of a yellow solid.
m.p. 121-123 °C.
^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (d, 2H), 7.48-7.55 (m, 3H), 7.32-7.43 (m, 4H), 6.26 (t, 1H), 5.48 (s, 2H), 4.66 (d, 2H, 3.02 (hept, 1H), 2.66 (t, 1H), 1.33 (d, 6H).
MS: 426 $(M+1)^+$

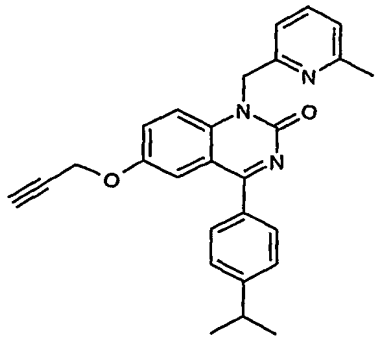
The compounds of the following examples are prepared by analogy to the example described above:

Example 41: 4-(4-Isopropyl-phenyl)-1-(5-methoxy-pyridin-2-ylmethyl)-6-propargyloxy-1H-quinazolin-2-one, m. p. 136-137 °C.



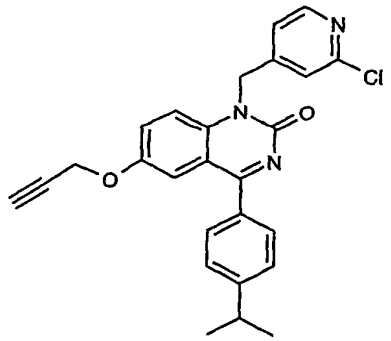
^{1}H-NMR (300 MHz, $CDCl_3$): 8.25 (dd, 1H), 7.68-7.74 (m, 3H), 7.42-7.48 (m, 2H), 7.34-7.41 (m, 3H), 7.14 (dd, 1H), 5.60 (broad, 2H), 4..65 (d, 2H), 3.84 (s, 3H), 3.02 (hept, 1H), 2.65 (t, 1H), 1.33 (d, 6H).
MS: 440 $(M+1)^+$

Example 42: 4-(4-Isopropyl-phenyl)-1-(6-methyl-pyridin-2-ylmethyl)-6-propargyloxy-1H-quinazolin-2-one, m. p. 165-166 °C



^{1}H-NMR (300 MHz, $CDCl_3$): 7.75 (d, 2H), 7.45-7.55 (m, 3H), 7.38 (d, 2H), 7.34 (dd, 1H), 7.10 (d, 1H), 7.05 (d, 1H), 5.62 (broad, 2H), 4..65 (d, 2H), 3.02 (hept, 1H), 2.60 (s, 3H), 2.55 (t, 1H), 1.33 (d, 6H).
MS: 424 $(M+1)^+$

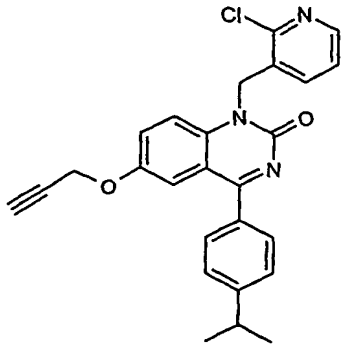
Example 43:1-(2-Chloro-pyridin-4-ylmethyl)-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



^{1}H-NMR (300 MHz, $CDCl_3$): 8.35 (d, 1H), 7.77 (d, 2H), 7.57 (d, 1H), 7.41 (d, 2H), 7.37 (dd, 1H), 7.24 (s, 1H), 7.16 (d, 1H), 7.06 (d, 1H), 5.62 (broad s, 2H), 4.67 (d, 2H), 3.04 (hept, 1H), 2.57 (t, 1H), 1.34 (d, 6H).

MS: 444 $(M+1)^+$

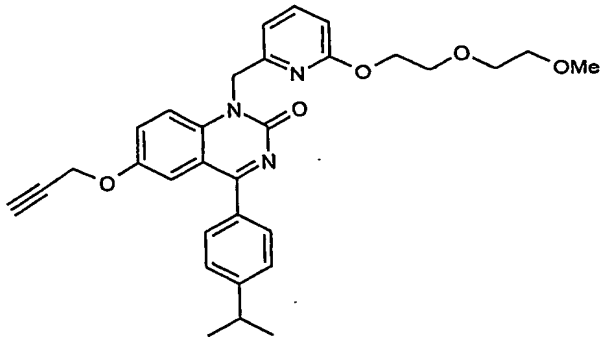
Example 44: 1-(2-Chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-propargyloxy-1H-quinazolin-2-one



^{1}H-NMR (300 MHz, $CDCl_3$): 8.84 (d, 1H), 7.77 (d, 2H), 7.65 (d, 1H), 7.41 (d, 2H), 7.31-7.39 (m, 2H), 7.16 (dd, 1H), 7.07 (d, 1H), 5.61 (s, 2H), 4.67 (d, 2H), 3.91 (broad, 2H), 3.04 (hept, 1H), 2.56 (t, 1H), 1.33 (d, 6H).

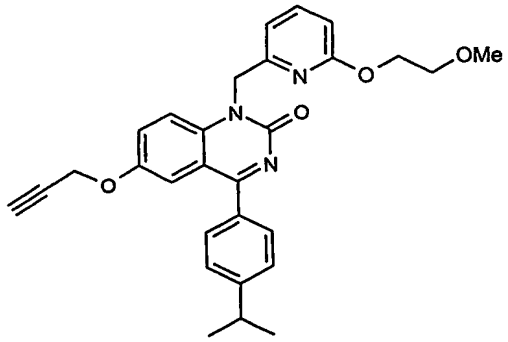
MS: 444 $(M+1)^+$

Example 45: 4-(4-Isopropyl-phenyl)-1-{6-[2-(2-methoxy-ethoxy)-ethoxy]-pyridin-2-ylmethyl)-6-propargyloxy-1H-quinazolin-2-one



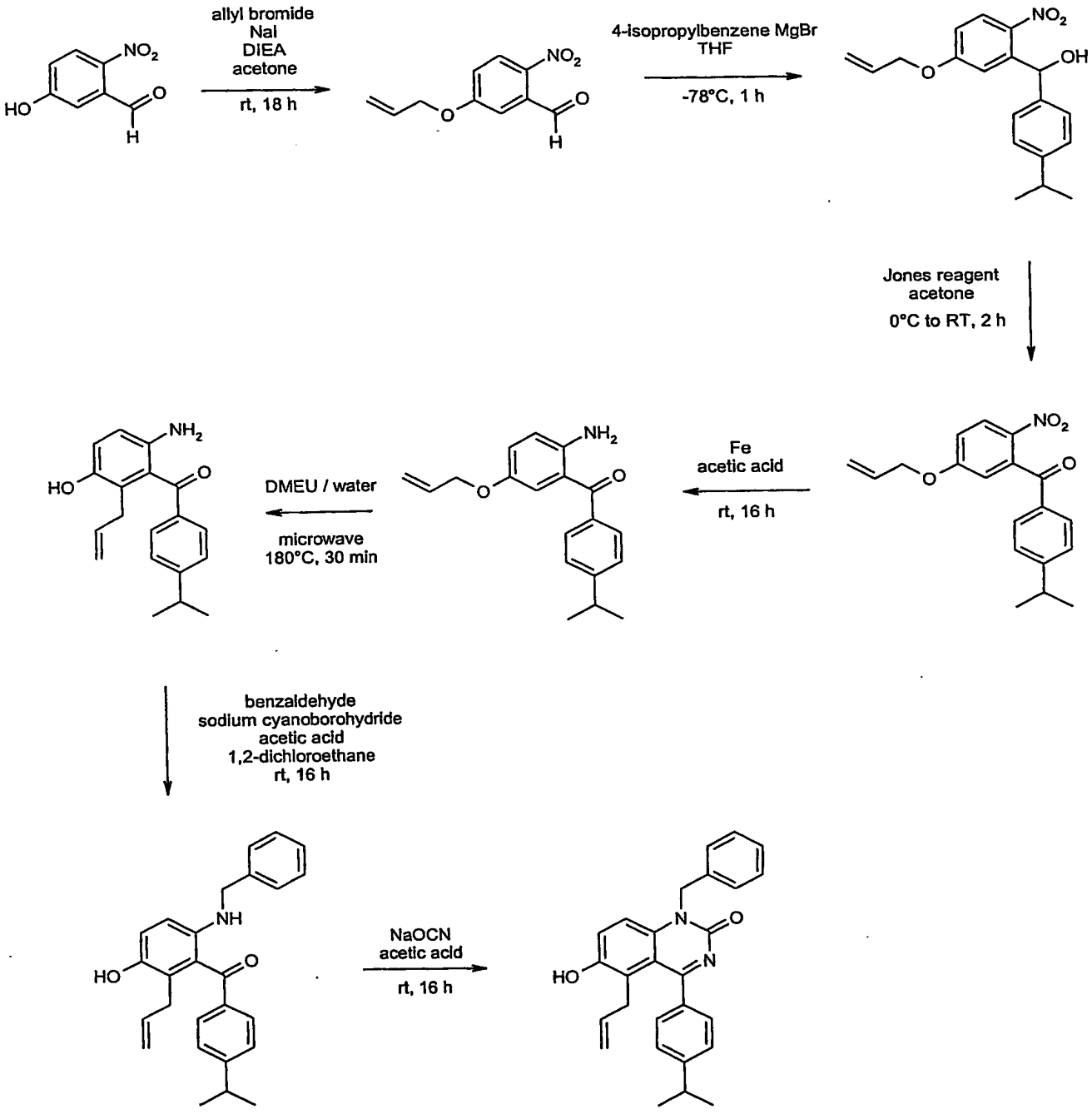
^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (d, 2H), 7.47-7.65 (m, 3H), 7.38 (d, 2H), 7.35 (dd, 1H), 6.93 (d, 1H), 6.66 (d, 1H), 5.52 (broad, 2H), 4.66 (d, 2H), 4.41 (dd, 2H), 3.78 (dd, 2H), 3.79 (dd, 2H), 3.65-3.71 (m, 2H), 3.54-3.60 (m, 2H), 3.39 (s, 3H), 3.02 (hept, 1H), 2.57 (t, 1H), 1.33 (d, 6H).
MS: 528 $(M+1)^+$

Example 46: 4-(4-Isopropyl-phenyl)-1-[6-(2-methoxy-ethoxy)-ethoxy)-pyridin-2-ylmethyl)-6-propargyloxy-1H-quinazolin-2-one

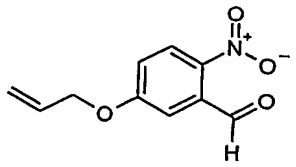


^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (d, 2H), 7.47-7.63 (m, 3H), 7.39 (d, 2H), 7.34 (dd, 1H), 6.92 (d, 1H), 6.69 (d, 1H), 5.53 (broad, 2H), 4.66 (d, 2H), 4.38-4.43 (m, 2H), 3.66-3.71 (m, 2H), 3.42 (s, 3H), 3.02 (hept, 1H), 2.56 (t, 1H), 1.33 (d, 6H).
MS: 484 $(M+1)^+$

Example 47: 5-Allyl-1-benzyl-6-hydroxy-4-(4-isopropyl-phenyl)-1H-quinazolin-2-one



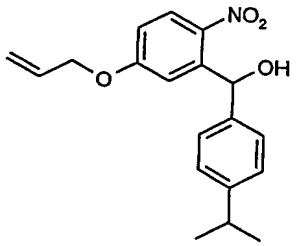
A. Synthesis of 5-allyloxy-2-nitro-benzaldehyde



To a solution of 25 g (150 mmol) 5-hydroxy-2-nitro-benzaldehyde and 44.8 g (299 mmol) sodium iodide in 400 ml acetone are added 51.2 ml (299 mmol) N-ethyldiisopropylamine and 25.3 ml (299 mmol) allyl bromide. After stirring for 18 h at r.t. the reaction mixture is filtered and the solvent is evaporated. Extraction of the residue with 1 M aqueous hydrochloric acid / dichloromethane followed by chromatography (hexane / ethyl acetate) yields 5-allyloxy-2-nitro-benzaldehyde.

^{1}H NMR (300 MHz, $CDCl_3$): 10.45 (s, 1H), 8.15 (d, 1H), 7.32 (d, 1H), 7.16 (dd, 1H), 6.03 (ddt, 1H), 5.45 (dq, 1H), 5.37 (dq, 1H), 4.69 (dt, 2H).

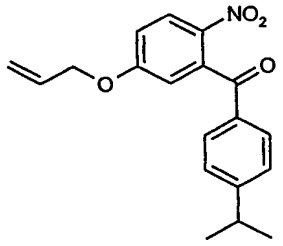
B. Synthesis of (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanol



A solution of 4-isopropylphenylmagnesium bromide prepared from 2.35 g (96.5 mmol) magnesium and 18.15 g (96.5 mmol) 1-bromo-4-isopropylbenzene in 80 ml THF is added slowly at –78 °C to a solution of 20 g (96.5 mmol) 5-allyloxy-2-nitro-benzaldehyde in 200 ml THF. After allowing the reaction mixture to warm up to r.t. saturated aqueous ammonium chloride solution is added. Extraction with ethyl acetate followed by chromatographic purification on silica (hexane / ethyl acetate) yields (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanol.

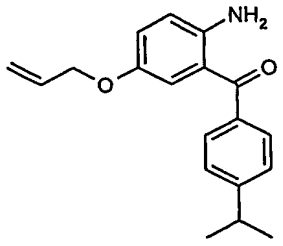
^{1}H NMR (300 MHz, $CDCl_3$): 8.05 (d, 1H), 7.34 (d, 1H), 7.25 (d, 2H), 7.16 (d, 2H), 6.88 (dd, 1H), 6.50 (s, 1H), 6.01 (ddt, 1H), 5.40 (d, 1H), 5.33 (d, 1H), 4.62 (d, 2H), 2.88 (hept, 1H), 1.22 (d, 6H).
MS: 310 $(M\text{-}OH)^+$

C. Synthesis of (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanone



A solution of 16.38 g (50 mmol) (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanol in 60 ml acetone is treated at 0 °C with 20 ml (53.4 mmol) Jones reagent. After stirring for 2 h at r.t. isopropanol, an aqueous solution of sodium bisulfite and saturated aqueous ammonium chloride solution are added. Extraction with dichloromethane affords (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanone.
^{1}H NMR (300 MHz, $CDCl_3$): 8.24 (d, 1H), 7.69 (d, 2H), 7.30 (d, 2H), 7.09 (dd, 1H), 6.89 (d, 1H), 6.03 (ddt, 1H), 5.43 (dq, 1H), 5.36 (dq, 1H), 4.65 (dt, 2H), 2.97 (hept, 1H), 1.27 (d, 6H).

D. Synthesis of (5-allyloxy-2-amino-phenyl)-(4-isopropyl-phenyl)-methanone



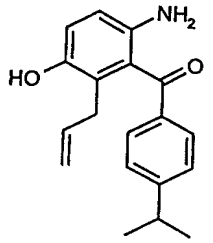
To an ice chilled solution of 16 g (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanone in 65 ml acetic acid are added 21.8 g iron powder. A precipitate that is formed is brought into solution by addition of additional acetic acid. After stirring for 16 h at r.t.

the reaction mixture is filtered and basified by addition of aqueous potassium hydroxide solution. Extraction with dichloromethane yields (5-allyloxy-2-amino-phenyl)-(4-isopropyl-phenyl)-methanone.

^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (d, 2H), 7.31 (d, 2H), 7.03 – 6.98 (m, 2H), 6.71 (d, 1H), 5.98 (ddt, 1H), 5.32 (dd, 1H), 5.25 (dd, 1H), 4.39 (d, 2H), 2.99 (hept, 1H), 1.31 (d, 6H).

MS: 296 $(M+1)^+$

E. Synthesis of (2-allyl-6-amino-3-hydroxy-phenyl)-(4-isopropyl-phenyl)-methanone

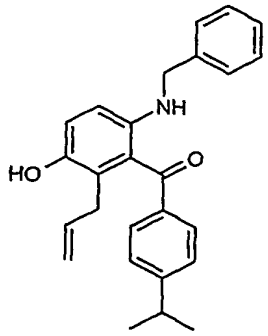


In a sealed tube a mixture of 50 mg (0.17 mmol) (5-allyloxy-2-nitro-phenyl)-(4-isopropyl-phenyl)-methanone, 1 ml DMEU and 1 ml water is heated by microwave irradiation to 180°C for 30 min. Water is evaporated and the resulting solution is purified by reversed phase preparative HPLC to yield the rearranged product.

^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (d, 2H), 7.30 (d, 2H), 6.81 (d, 1H), 6.60 (d, 1H), 5.80 (ddt, 1H), 5.03 (dq, 1H), 5.01 (dq, 1H), 3.16 (dt, 2H), 2.97 (hept, 1H), 1.28 (d, 6H).

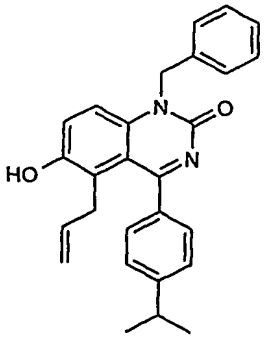
MS: 296 $(M+1)^+$

F. Synthesis of (2-allyl-6-benzylamino-3-hydroxy-phenyl)-(4-isopropyl-phenyl)-methanone



To a solution of 39 mg (0.13 mmol) (2-allyl-6-amino-3-hydroxy-phenyl)-(4-isopropyl-phenyl)-methanone and 13.34 µl (13 mmol) benzaldehyde in 1.3 ml 1,2-dichlorethane and 0.3 g molecular sieves (4 Å pore size) are added after 1 h 13 mg (0.18 mmol) sodium cyanoborohydride and 7.55 µl acetic acid (0.13 mmol). After stirring for 16 h at r.t. 1 M hydrochloric acid is added to destroy the excess of hydride equivalents. By adding 1 M NaOH the mixture was basified. The crude product obtained by extraction with dichloromethane is purified by reversed phase preparative chromatography.
^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.31 (d, 2H), 7.28 – 7.16 (m, 5H), 6.82 (d, 1H), 6.56 (d, 1H), 5.79 (ddt, 1H), 5.02 (dd, 1H), 5.01 (dd, 1H), 4.22 (s, 2H), 3.17 (d, 2H), 2.99 (hept, 1H), 1.30 (d, 6H).
MS: 386 $(M+1)^+$

G. Synthesis of 5-allyl-1-benzyl-6-hydroxy-4-(4-isopropyl-phenyl)-1H-quinazolin-2-one



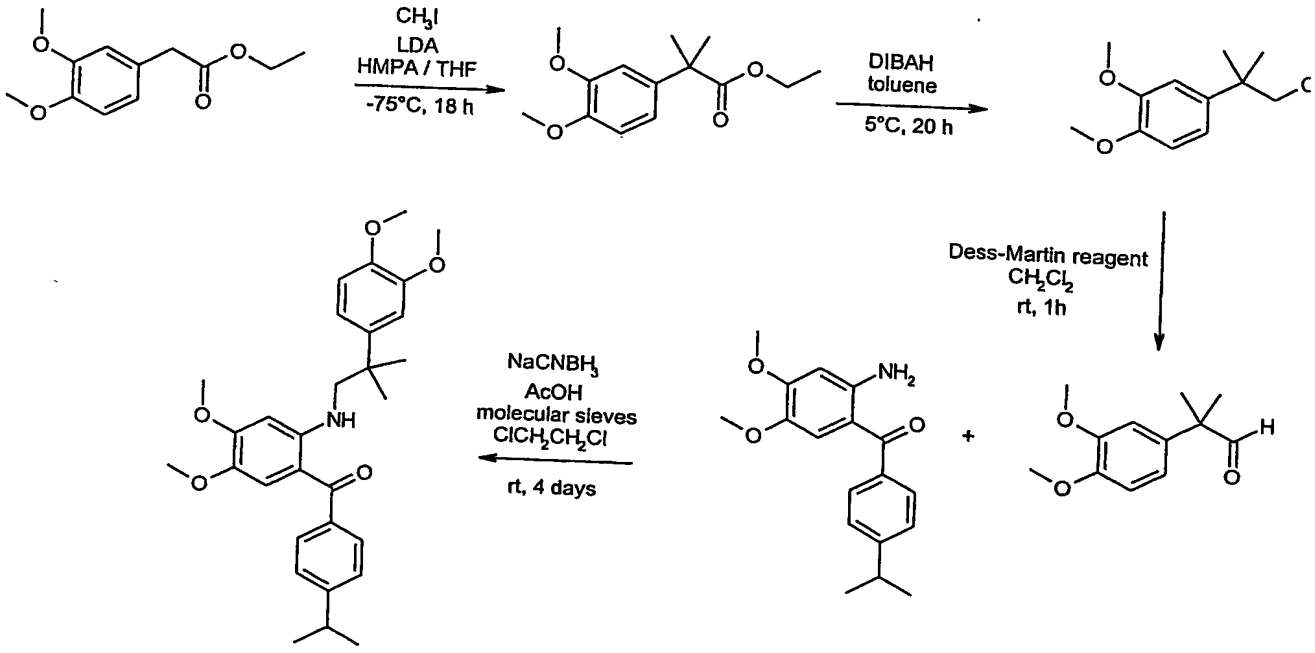
A solution of 15 mg (39 µmol) (2-allyl-6-benzylamino-3-hydroxy-phenyl)-(4-isopropyl-phenyl)-methanone and 2.5 mg sodium cyanate in 0.2 ml acetic acid is stirred at r.t. for 16

h. Aqueous sodium hydroxide solution is added and the product is extracted with dichloromethane.

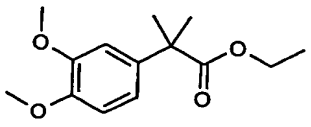
^{1}H NMR (300 MHz, $CDCl_3$): 7.48 (d, 2H), 7.33 – 7.24 (m, 8H), 7.14 (d, 1H), 5.65 (ddt, 1H), 5.52 (s, 2H), 5.10 (dd, 1H), 4.95 (dd, 1H), 3.20 (d, 2H), 2.97 (hept, 1H), 1.28 (d, 6H).

MS: 411 $(M+1)^+$

Example 48: {2-[2-(3,4-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone



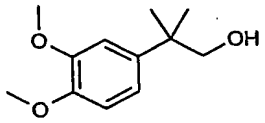
A. Synthesis of 2-(3,4-dimethoxy-phenyl)-2-methyl-propionic acid ethyl ester



A solution of 2.00 g (8.92 mmol) ethyl-3,4-dimethoxyphenyl acetate, 2.85 ml (17.84 mmol) HMPA and 3.34 ml (53.52 mmol) methyl iodide in 50 ml THF is treated at –75°C with 51.9 ml (35.7 mmol) of a LDA solution prepared in THF. After 18 h stirring at –75°C the cold reaction mixture is poured into an aqueous saturated ammonium chloride solution and extracted with ethyl acetate. After evaporation the crude dimethylated compound still containing some HMPA is obtained and is directly further transformed as described below.

^{1}H NMR (300 MHz, $CDCl_3$): 6.88 (dd, 1H), 6.86 (d, 1H), 6.82 (d, 1H), 4.12 (q, 2H), 3.87 (s, 3H), 3.87 (s, 3H), 1.57 (s, 6H), 1.20 (t, 3H).

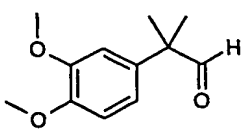
B. Synthesis of 2-(3,4-dimethoxy-phenyl)-2-methyl-propan-1-ol



A solution of 909 mg (ca. 2 mmol) of the crude product described directly above in 5 ml toluene is treated twice with 2.69 ml (3.2 mmol) of 1.2 M DIBAH solution in toluene at 5°C. After stirring for 20 h saturated ammonium chloride solution is added. The reaction mixture is filtered and extracted with diethyl ether to obtain after evaporation of the solvent 2-(3,4-dimethoxy-phenyl)-2-methyl-propan-1-ol.

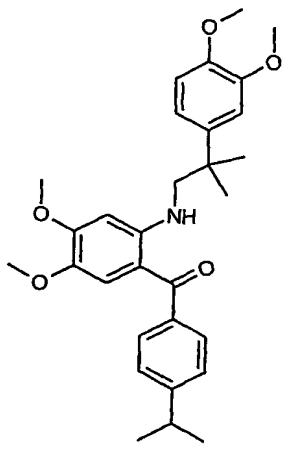
^{1}H NMR (300 MHz, $CDCl_3$): 6.94 –6.91 (m, 2H), 6.85 (d, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.60 (s, 2H), 1.34 (s, 6H).

C. Synthesis of 2-(3,4-dimethoxy-phenyl)-2-methyl-propionaldehyde



A solution of 100 mg (0.476 mmol) 2-(3,4-dimethoxy-phenyl)-2-methyl-propan-1-ol in 1 ml dichloromethane is treated with 202 mg (0.476 mmol) Dess-Martin reagent at rt. After 1 h aqueous sodium bicarbonate and sodium thiosulphate solutions are added and the product is extracted with dichloromethane. The organic layers are evaporated and the aldehyde is obtained in a sufficient purity to be used in reductive aminations.
^{1}H NMR (300 MHz, $CDCl_3$): 9.44 (s, 1H), 6.88 (d, 1H), 6.83 (dd, 1H), 6.74 (d, 1H), 3.88 (s, 6H), 1.46 (s, 6H).

D. Synthesis of {2-[2-(3,4-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone



After one hour stirring a mixture of 143 mg (0.476 mmol) (2-amino-4,5-dimethoxy-phenyl)-(4-isopropyl-phenyl)-methanone, 98 mg (0.476 mmol) 2-(3,4-dimethoxy-phenyl)-2-methyl-propionaldehyde, 1.1 g molecular sieves 4 Å pore size, 5 ml 1,2-dichloroethane and 31 µl (0.476 mmol) acetic acid 41 mg (0.666 mmol) $NaCNBH_3$ are added. Over the duration of 4 days three additional portions of 31 µl acetic (0.476 mmol) and 41 mg $NaCNBH_3$ (0.666 mmol) are added. Excess hydride is destroyed by addition of 1 M hydrochloric acid and the reaction mixture is basified by means of 1 M sodium hydroxide. {2-[2-(3,4-Dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-

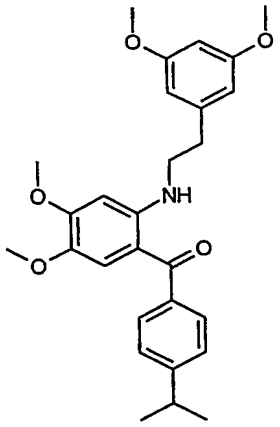
phenyl}-(4-isopropyl-phenyl)-methanone is isolated by filtration followed by extraction with dichloromethane and reversed phase preparative HPLC.

^{1}H NMR (300 MHz, $CDCl_3$): 7.50 (d, 2H), 7.28 (d, 2H), 7.13 – 7.00 (m, 3H), 6.84 (d, 1H), 6.14 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 3.35 (s, 2H), 2.97 (hept, 1H), 1.52 (s, 6H), 1.29 (d, 6H).

MS: 492 $(M+1)^+$

The compounds of the following examples is prepared by analogy to the example described above:

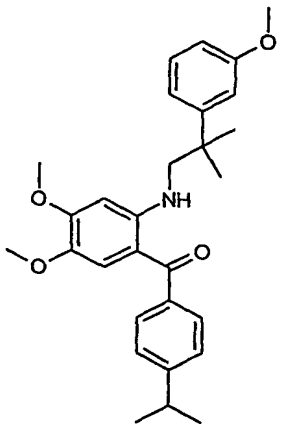
Example 49: {2-[2-(3,5-Dimethoxy-phenyl)-ethylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone



^{1}H NMR (300 MHz, $CDCl_3$): 7.53 (d, H), 7.30 (d, 2H), 7.06 (s, 1H), 6.46 (d, 2H), 6.35 (t, 1H), 6.22 (s, 1H), 3.93 (s, 3H), 3.79 (s, 6H), 3.68 (s, 3H), 3.50 (t, 2H), 3.03 – 2.94 (m, 3H), 1.31 (d, 6H).

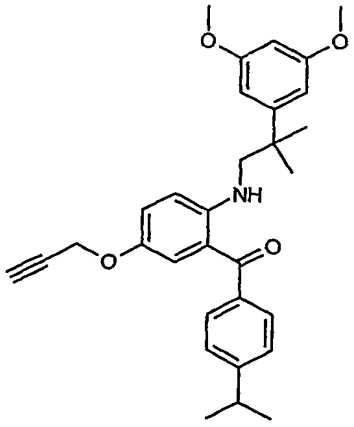
MS: 464 $(M+1)^+$

Example 50: {4,5-Dimethoxy-2-[2-(3-methoxy-phenyl)-2-methyl-propylamino]-phenyl}-(4-isopropyl-phenyl)-methanone



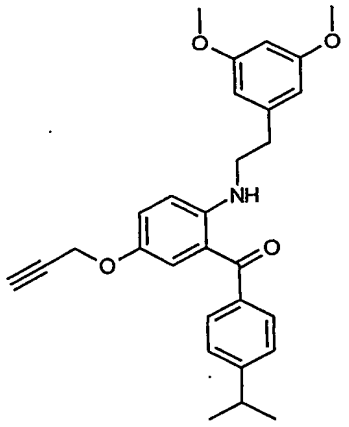
^{1}H NMR (300 MHz, $CDCl_3$): 7.51 (d, 2H), 7.29 (d, 2H), 7.25 (t, 1H), 7.05 (m, 1H), 7.02 (s, 1H), 6.99 (t, 1H), 6.75 (dd, 1H), 6.30 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.40 (s, 2H), 1.53 (s, 6H), 1.30 (d, 6H).
MS: 462 $(M+1)^+$

Example 51: {2-[2-(3,5-Dimethoxy-phenyl)-2-methyl-propylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone



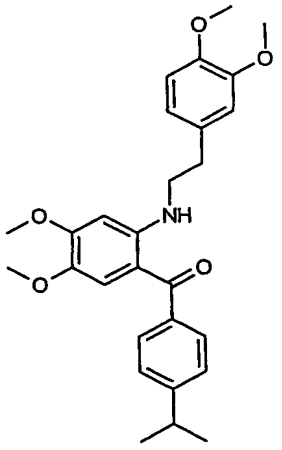
^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (d, 2H), 7.28 (d, 2H), 7.16 (d, 1H), 7.11 (dd, 1H), 6.87 (d, 1H), 6.68 (d, 2H), 6.30 (s, 1H), 4.54 (d, 2H), 3.77 (s, 6H), 3.36 (s, 2H), 2.98 (hept, 1H), 2.48 (t, 1H), 1.48 (s, 6H), 1.30 (d, 6H).
MS: 486 $(M+1)^+$

Example 52: {2-[2-(3,5-Dimethoxy-phenyl)-ethylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone



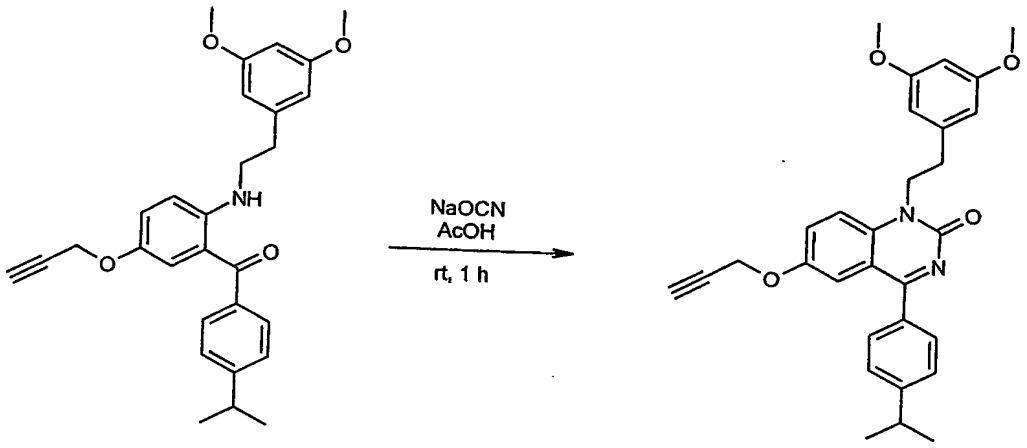
^{1}H NMR (300 MHz, $CDCl_3$): 7.59 (d, 2H), 7.30 (d, 2H), 7.20 (d, 1H), 7.15 (dd, 1H), 6.82 (d, 1H), 6.44 (d, 2H), 6.84 (t, 1H), 4.55 (d, 2H) 3.79 (s, 6H), 3.48 (t, 2H). 3.03 – 2.93 (m, 3H), 2.49 (t, 1H), 1,31 (d, H).
MS: 458 $(M+1)^+$

Example 53: {2-[2-(3,4-Dimethoxy-phenyl)-ethylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone



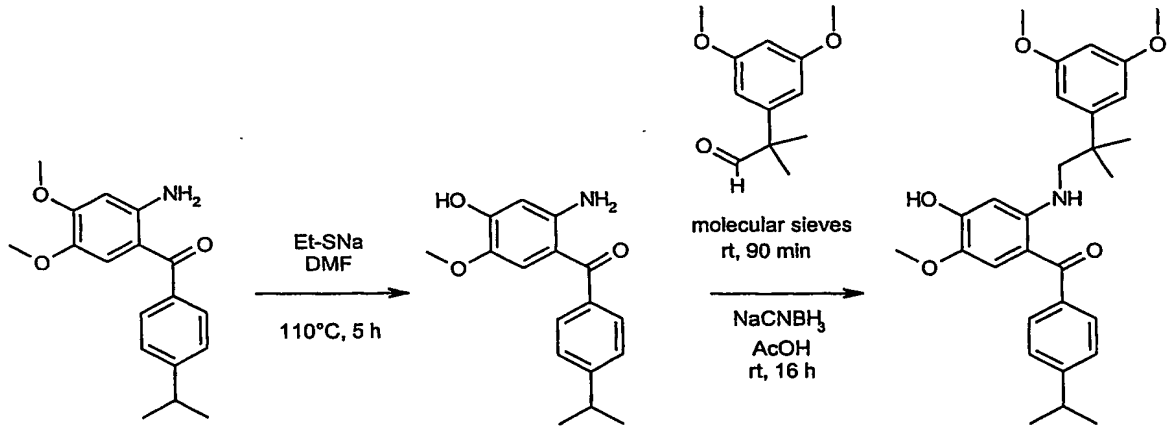
^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (d, 2H), 7.32 (d, 2H), 7.08 (s, 1H), 6.84 – 6.83 (m, 3H), 6.67 (broad, 1H), 3.97 (s, 3H); 3.87 (s, 3H), 3.87 (s, 3H), (3.72 s, 3H), 3.49 (t, 2H), 3.08 (t, 2H), 2.99 (hept, 1H), 1.31 (d, 6H).
MS: 464 $(M+1)^+$

Example 54: 1-[2-(3,5-Dimethoxy-phenyl)-ethyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one

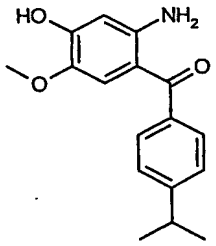


A solution of 15 mg (33 µmol) {2-[2-(3,5-dimethoxy-phenyl)-ethylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone and 2.1 mg (33 µmol) NaOCN in 300 µl acetic acid is stirred for 1 h at rt. The solvent is evaporated and the product is recrystallised from CH_2Cl_2 /diethyl ether.
^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (d, 2H), 7.49 (d, 1H), 7.43 (dd, 1H), 7.37 (d, 2H), 7.34 (d, 1H), 6.50 (d, 2H), 6.36 (t, 1H), 4.68 (d, 2H), 4.48 (dd, 2H), 3.80 (s, 6H), 3.09 – 2.97 (m, 3H), 2.57 (t, 1H), 1.32 (d, 6H).
MS: 483 $(M+1)^+$

Example 55: {2-[2-(3,5-Dimethoxy-phenyl)-2-methyl-propylamino]-4-hydroxy-5-methoxy-phenyl}-(4-isopropyl-phenyl)-methanone



A. Synthesis of (2-amino-4-hydroxy-5-methoxy-phenyl)-(4-isopropyl-phenyl)-methanone

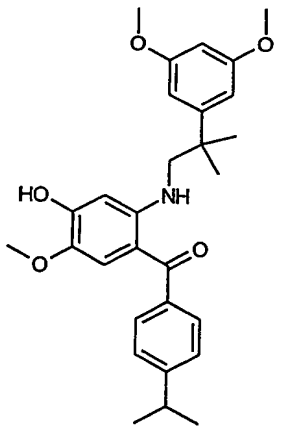


A mixture of 1.34 g (4.48 mmol) (2-amino-4,5-dimethoxy-phenyl)-(4-isopropyl-phenyl)-methanone, 1.88 g sodium ethanethiolate and 10 ml DMF are heated for 5h to 110°C. Saturated aqueous bicarbonate solution (10 ml) and 100 ml water are added. The product is extracted with CH_2Cl_2 and chromatographed on silica (hexane / ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): 7.56 (d, 2H), 7.30 (d, 2H), 6.96 (s, 1H), 6.31 (s, 1H), 3.70 (s, 3H), 1.30 (d, 6H).

MS: 286 $(M+1)^+$

B. Synthesis of {2-[2-(3,5-dimethoxy-phenyl)-2-methyl-propylamino]-4-hydroxy-5-methoxy-phenyl}-(4-isopropyl-phenyl)-methanone



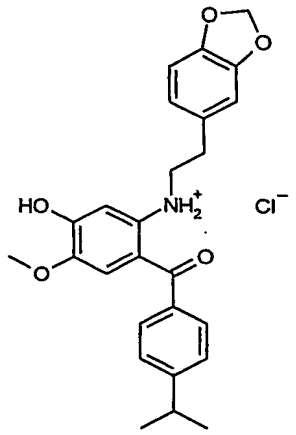
A mixture of 41.1 mg (144 µmol) (2-amino-4-hydroxy-5-methoxy-phenyl)-(4-isopropyl-phenyl)-methanone, 45 mg (216µmol) 2-(3,5-dimethoxy-phenyl)-2-methyl-propionaldehyde, 180 mg molecular sieves (pore size 4Å) and 0.50 ml CH_2Cl_2 is stirred for 90 min before 8.23 µl (144 µmol) and 22 mg $NaCNBH_3$ are added. After 16 h the excess of reducing agent is destroyed by addition of 1 M hydrochloric acid and the mixture is basified with 1 M sodium hydroxide solution. The product is extracted with CH_2Cl_2 and purified by reversed phase preparative HPLC.

^{1}H NMR (300 MHz, d_6DMSO): 10.07 (s, 1H), 8.71 (t, broad, 1H), 7.40 (d, 2H), 7.31 (d, 2H), 6.84 (s, 1H), 6.56 (d, 2H), 6.33 (t, 1H), 6.26 (s, 1H), 3.71 (s, 6H), 3.50 (s, 3H), 3.27 (d, 2H), 2.94 (hept, 1H), 1.35 (s, 6H), 1.23 (d, 6H).

MS: 478 $(M+1)^+$

The compound of the following example is prepared by analogy to the example described above:

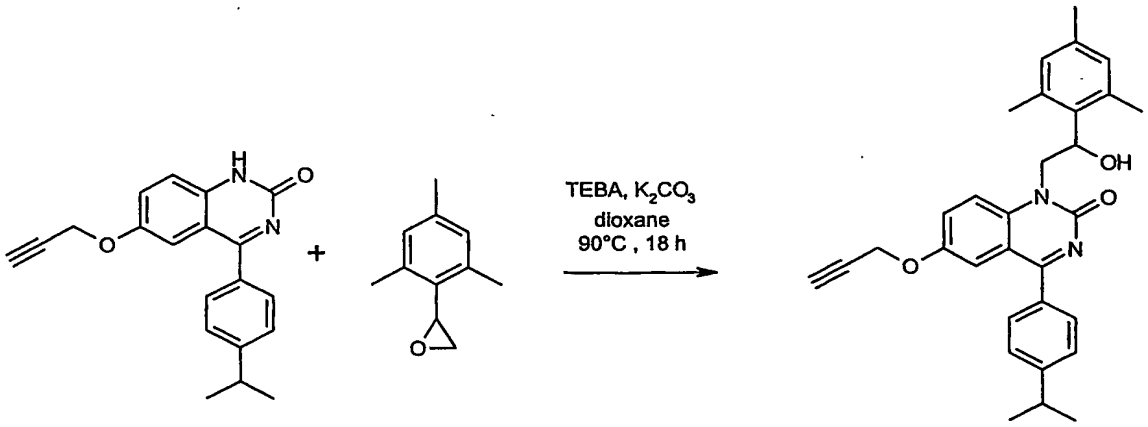
Example 56: (2-Benzo[1,3]dioxol-5-yl-ethyl)-[5-hydroxy-2-(4-isopropyl-benzoyl)-4-methoxy-phenyl]-ammonium; chloride



^{1}H NMR (300 MHz, CD_3OD): 7.71 (d, 2H), 7.44 (d, 2H), 7.19 (s, 1H), 6.98 (m, 1H), 6.79 (s, 1H), 6.75 (s, 2H), 5.90 (s, 2H), 3.79 (s, 3H), 3.63 (t, 2H), 3.08 – 2.99 (m, 3H), 1.32 (d, 6H).

MS: 434 $(M+1)^+$

Example 57: 1-[2-Hydroxy-2-(2,4,6-trimethyl-phenyl)-ethyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



A mixture of 0.5g (1.57 mmol) 4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 0.254 g (1.57 mmol) mesityl oxirane, 35.7 mg (0.157 mmol) benzyltriethylammonium chloride and 21.7 mg (0.157 mmol) potassium carbonate is

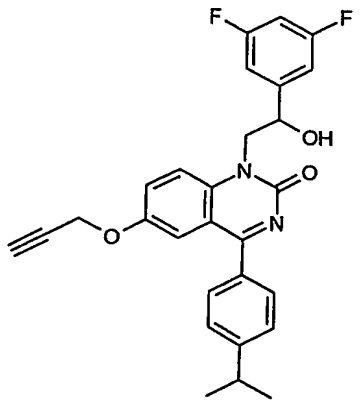
stirred in 1 ml dioxane at 90°C for 6 days. The reaction mixture is extracted with water / dichloromethane and, after evaporation of the organic phases, the residue is purified by preparative reversed phase HPLC.

^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (d, 2H), 7.54 (d, 1H), 7.50 (d, 1H), 7.43 (dd, 1H), 7.38 (d, 2H), 6.88 (s, 2H), 5.66 (dd, 1H), 4.93 (d, 1H), 4.68 (d, 2H), 4.37 (dd, 1H), 3.02 (hept, 1H), 2.60 (s, 6H), 2.57 (t, 1H), 2.28 (s, 3H), 1.33 (d, 6H).

MS: 481 $(M+1)^+$

The compound of the following example is prepared by analogy to the example described above:

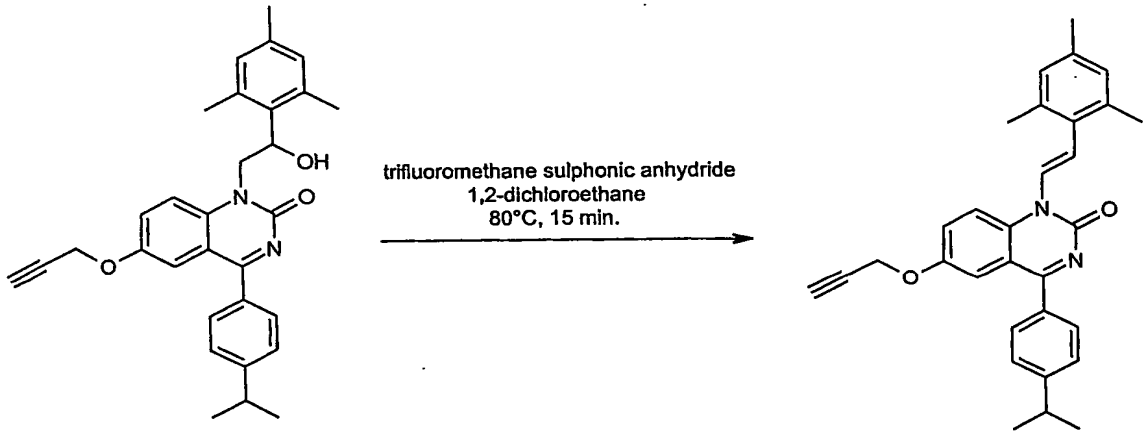
Example 58: 1-[2-(3,5-Difluoro-phenyl)-2-hydroxy-ethyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.67 (d, 2H), 7.49 – 7.43 (m, 3H), 7.37 (d, 2H), 7.10 (m, 2H), 6.74 (tt, 1H), 5.81 (dd, 1H), 4.68 (d, 2H), 4.51 (dd, 2H), 4.38 (dd, 2H), 3.01 (hept, 1H), 2.57 (t, 1H), 1.32 (d, 6H).

MS: 475 $(M+1)^+$

Example 59: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-[(E)-2-(2,4,6-trimethyl-phenyl)-vinyl]-1H-quinazolin-2-one

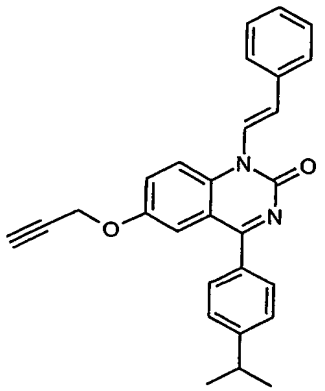


A solution of 50 mg (0.104 mmol) 1-[2-hydroxy-2-(2,4,6-trimethyl-phenyl)-ethyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one and 34.3 µl (0.208 mmol) trifluoromethane sulphonic anhydride in 0.5 ml 1,2 dichloroethane is heated to 80°C for 15 min. Extraction with dichloromethane / aqueous $NaHCO_3$ followed by preparative reversed phase HPLC yielded the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H), 7.68 (d, 1H), 7.51 (d, 1H), 7.41 (dd, 1H), 7.40 (d, 2H), 7.03 (d, 1H), 6.94 (s, 2H), 6.71 (d, 1H), 4.69 (d, 2H), 3.03 (hept, 1H), 2.58 (t, 1H), 2.47 (s, 6H), 2.32 (s, 3H), 1.33 (d, 6H).
MS: 463 $(M+1)^+$

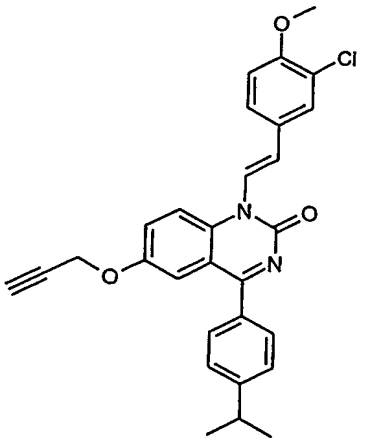
The compounds of the following examples are prepared by analogy to the example described above:

Example 60: 4-(4-Isopropyl-phenyl)-6-prop-2-ynyloxy-1-((E)-styryl)-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.64 (d, 1H), 7.56 – 7.53 (m, 2H), 7.51 (d, 1H), 7.43 – 7.35 (m, 6H), 7.25 (d, 1H), 7.03 (d, 1H), 4.70 (d, 2H), 3.03 (hept, 1H), 2.58 (t, 1H), 1.34 (d, 6H).
MS: 421 $(M+1)^+$

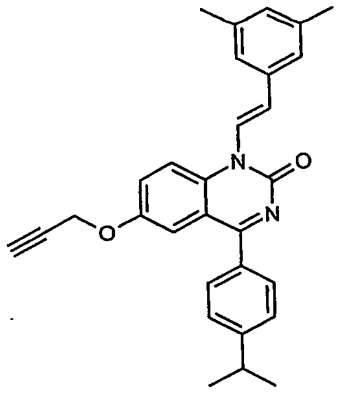
Example 61: 1-[(E)-2-(3-Chloro-4-methoxy-phenyl)-vinyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H NMR (300 MHz, $CDCl_3$): 7.77 (d, 2H), 7.60 (d, 1H), 7.59 (s, 1H), 7.51 (d, 1H), 7.41 – 7.37 (m, 4H), 7.13 (d, 1H), 6.96 (d, 1H), 6.92 (d, 1H), 4.70 (d, 2H), 3.95 (s, 3H), 3.03 (hept, 1H), 2.58 (t, 1H), 1.33 (d, 6H).

MS: 487 (30), 485 (100) $(M+1)^+$ (chlorine isotope pattern)

Example 62: 1-[(E)-2-(3,5-Dimethyl-phenyl)-vinyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one



^{1}H-NMR (300 MHz, $CDCl_3$): 7.78 (d, 2H), 7.64 (d, 1H), 7.50 (d, 1H), 7.40 (d, 2H), 7.37 (dd, 1H), 7.23 (d, 1H), 7.17 (s, 2H), 7.00 (s, 1H), 6.93 (d, 1H), 4.69 (d, 2H), 3.03 (hept, 1H), 2.58 (t, 1H), 2.36 (s, 6H), 1.33 (d, 6H).
MS: 449 $(M+1)^+$

The Agents of the Invention, as defined above, e.g., of formula I or II, particularly as exemplified, in free or pharmaceutically acceptable acid addition salt form, exhibit pharmacological activity and are useful as pharmaceuticals, e.g. for therapy, in the treatment of diseases and conditions as hereinafter set forth.

Inositol phosphate formation assay:

To determine antagonistic activity at the human parathyroid calcium-sensing receptor (PcaR), compounds were tested in functional assays measuring the inhibition of calcium-induced inositol phosphate formation in CCL39 fibroblasts stably transfected with human PcaR.

Cells were seeded into 24 well plates and grown to confluence. Cultures were then labelled with [^{3}H]inositol (74 Mbq/ml) in serum-free medium for 24h. After labelling, cells were washed once with a modified Hepes-buffered salt solution (mHBS: 130 mM NaCl, 5.4 mM KCl, 0.5 mM $CaCl_2$, 0.9 mM $MgSO_4$, 10 mM glucose, 20 mM HEPES, pH 7.4) and incubated with mHBS at 37 °C in the presence of 20 mM LiCl to block inositol monophosphatase activity. Test compounds were added 3 minutes before stimulating PcaR with 5.5 mM calcium and incubations continued for further 20 min. Thereafter, cells were extracted with 10 mM ice-cold formic acid and inositol phosphates formed were determined using anion exchange chromatography and liquid scintillation counting.

Assay for intracellular free calcium:

An alternative method to determine antagonism at the PcaR consists in measuring the inhibition of intracellular calcium transients stimulated by extracellular calcium. CCL39 fibroblasts stably transfected with human PcaR were seeded at 40'000 cells /well into 96-well Viewplates and incubated for 24 hours. Medium was then removed and replaced with fresh medium containing 2 µM Fluo-3 AM (Molecular Probes, Leiden, The Netherlands), In routine experiments, cells were incubated at 37°C, 5 % CO_2 for 1 h. Afterwards, plates were washed twice with mHBS and wells were refilled with 100 µl mHBS containing the test compounds. Incubation was continued at room temperature for 15 minutes. To record changes of intracellular free calcium, plates were transferred to fluorescence-imaging plate reader (Molecular Devices, Sunnyvale, CA, USA). A baseline consisting in 5 measurements of 0.4 seconds each (laser excitation 488 nm) was recorded. Cells were then stimulated with calcium (2.5 mM final), and fluorescence changes recorded over a period of 3 minutes.

When measured in the above assays, Agents of the Invention typically have IC_{50}s in the range from about 50 µM down to about 10 nM or less.

It is now well established that controlled treatment of patients with parathyroid hormone (PTH) and analogues and fragments thereof can have a pronounced anabolic effect on bone formation. Thus compounds which promote PTH release, such as the Agents of the Invention may be used for preventing or treating conditions of bone which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.

Thus in a further aspect the invention includes a method for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable in which an effective amount of an Agent of the Invention is administered to a patient in need of such treatment.

In a yet further aspect the invention includes a pharmaceutical composition for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable comprising an Agent of the Invention in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

Agents of the Invention are accordingly indicated for preventing or treating all bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable, e.g. osteoporosis of various genesis (e.g. juvenile, menopausal, post-menopausal, post-traumatic, caused by old age or by corticosteroid therapy or inactivity), fractures, osteopathy, including acute and chronic states associated with skeletal demineralisation, osteo-malacia, periodontal bone loss or bone loss due to arthritis or osteoarthritis or for treating hypoparathyroidism.

Further diseases and disorders which might be prevented or treated include e.g. seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage such as in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, congestive heart failure; hypertension; gut motility disorders such as diarrhoea, and spastic colon and dermatological disorders, e.g. in tissue healing, for example burns, ulcerations and wounds.

The Agents of the Invention are particularly indicated for preventing or treating osteoporosis of various genesis.

For all the above uses, an indicated daily dosage is in the range from about 0.03 to about 300 mg preferably 0.03 to 30, more preferably 0.1 to 10 mg of a compound of the invention. Agents of the Invention may be administered twice a day or up to twice a week.

The Agents of the Invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds. The present invention also provides a pharmaceutical composition comprising an Agent of the Invention in free base form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. The Agents of the Invention may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules or in a transdermal, nasal or a suppository form.

In accordance with the foregoing the present invention further provides:

1. an Agent of the Invention or a pharmaceutically acceptable salt thereof for use as a pharmaceutical;

1. a method for preventing or treating above mentioned disorders and diseases in a subject in need of such treatment, which method comprises administering to said subject an effective amount of an Agent of the Invention or a pharmaceutically acceptable salt thereof;

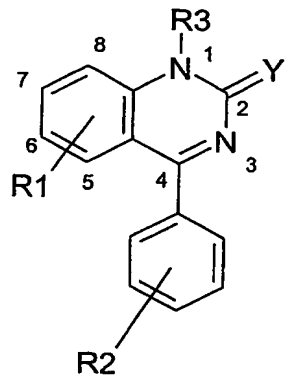
c) an Agent of the Invention or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition e.g. for use in the method as in b) above.

According to a further embodiment of the invention, the Agents of the Invention may be employed as adjunct or adjuvant to other therapy, e.g. a therapy using a bone resorption inhibitor, for example as in osteoporosis therapy, in particular a therapy employing calcium, a calcitonin or an analogue or derivative thereof, e.g. salmon, eel or human calcitonin, a steroid hormone, e.g. an estrogen, a partial estrogen agonist or estrogen-gestagen combination, a SERM (Selective Estrogen Receptor Modulator) e.g. raloxifene, lasofoxifene, TSE-424, FC1271, Tibolone (Livial ®), vitamin D or an analogue thereof or PTH, a PTH fragment or a PTH derivative e.g. PTH (1-84), PTH (1-34), PTH (1-36), PTH (1-38), PTH (1-31)NH_2 or PTS 893.

When the Agents of the Invention are administered in conjunction with, e.g. as an adjuvant to bone resorption inhibition therapy, dosages for the co-administered inhibitor will of course vary depending on the type of inhibitor drug employed, e.g. whether it is a steroid or a calcitonin, on the condition to be treated, whether it is a curative or preventive therapy, on the regimen and so forth.

CLAIMS

1. A compound of formula I



I

wherein Y is O or S;

R1 represents from 1 to 3 substituents independently selected from OH, SH, halo, NO_2, optionally substituted (lower alkyl, lower alkoxy, lower alkenyl, lower alkenyloxy, lower alkynyl, lower alkynyloxy, lower alkanoyl, lower alkylsulphone, lower alkylsulphoxide or amino);

R2 represents from 1 to 3 substituents selected from halo, optionally substituted (lower alkyl, lower alkenyl, cycloalkyl, lower alkoxy or amino);

R3 is

A) lower alkyl substituted by 1 to 3 substituents independently selected from lower alkylene, Br, F, CF_3 or $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2,

B) Benzyl which is

   a. mono-or di- (preferably mono-) substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x, y and z are as defined above,

   b. morpholino-lower alkoxy, aryl-lower alkoxy or optionally N-lower alkyl substituted arylamino-lower alkoxy,

c. substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy,

d. substituted on the $-CH_2-$ group thereof,

C) optionally substituted (aryl-C_2-C_8-alkyl, aryl- C_2-C_8-alkenyl, heteroarylmethyl or 4-heteroarylbenzyl); or

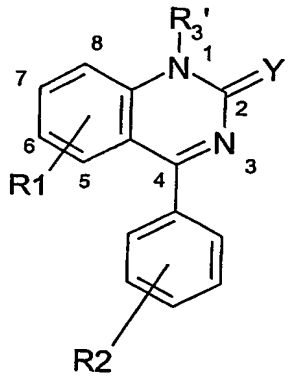
when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3 is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);

provided the compound of formula I is not 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-3-ylmethyl-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-2-ylmethyl-1.H.-quinazolin-2-one, 1-(6-chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-(5-nitro-furan-2-ylmethyl)-1.H.-quinazolin-2-one or 1-[2-(1.H.-indol-2-yl)-ethyl]-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-phenethyl-1H-quinazolin-2-one, 1-(2hydroxy-2-phenyl-ethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, methanesulfonic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-phenyl ester, or acetic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-yl]-1-phenyl-ethyl ester, 5-allyl-6-hydroxy-1-isopropyl-4-(4-isopropyl-phenyl)-1.H.-quinazolin-2-one;

a compound selected from 4-(4-isopropyl-phenyl)-1-(3,4-diamino-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-(2,6-dichloro-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-benzyl-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione, 1-(3di-tert-butyl-4-hydroxy-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, or 1-[3-(2-hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

2. A compound according to claim 1 of formula I'



I'

wherein Y is O or S;

R1 and R2 are as defined above for formula I;

R3' is

A) lower alkyl substituted by 1 to 3 substituents independently selected from –S-lower alkyl, lower alkylene, Br, F or CF_3,

B) benzyl which is

d. mono-or di- (preferably mono-) substituted by $-O_x-(CH_2)_y-SO_z$-lower alkyl, wherein x is 0 or 1, y is 0, 1 or 2 and z is 0, 1 or 2,

e. morpholino-lower alkoxy, aryl-lower alkoxy or optionally N-lower alkyl substituted arylamino-alkoxy,

f. substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy,

C) optionally substituted (arylvinyl, arylethyl, heteroarylmethyl or 4-heteroarylbenzyl) ; or

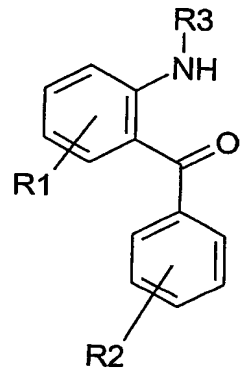
when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3 is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);

provided the compound of formula I is not 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-3-ylmethyl-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-pyridin-2-ylmethyl-1.H.-quinazolin-2-one, 1-(6-chloro-pyridin-3-ylmethyl)-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-(5-nitro-furan-2-ylmethyl)-1.H.-quinazolin-2-one or 1-[2-(1.H.-indol-2-yl)-ethyl]-4-(4-isopropyl-phenyl)-6-methoxy-1.H.-quinazolin-2-one, 4-(4-isopropyl-phenyl)-6-methoxy-1-phenethyl-1H-quinazolin-2-one, 1-(2hydroxy-2-phenyl-ethyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, methanesulfonic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-ylmethyl]-phenyl ester, or acetic acid 2-[4-(4-isopropyl-phenyl)-2-oxo-6-prop-2-ynyloxy-2H-quinazolin-1-yl]-1-phenyl-ethyl ester, 5-allyl-6-hydroxy-1-isopropyl-4-(4-isopropyl-phenyl)-1.H.-quinazolin-2-one;

a compound selected from 4-(4-isopropyl-phenyl)-1-(3,4-diamino-benzyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-(2,6-dichloro-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, 1-benzyl-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione, 1-(3di-tert-butyl-4-hydroxy-benzyl)-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazolin-2-one, or 1-[3-(2-hydroxy-ethoxy)-benzyl]-4-(4-isopropyl-phenyl)-6-prop-2-ynyloxy-1H-quinazoline-2-thione;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

3. A compound of formula II



II

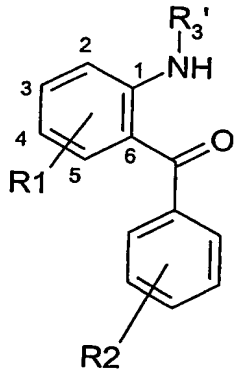
wherein R1, R2 and R3 are as defined above;

provided that the compound of formula II is not {2-[2-(3,5-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-3-ylmethyl)-amino]-phenyl}-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-2-ylmethyl)-amino]-phenyl}-methanone;

{2-[2-(2-hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone or {2-[(2,3-dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone;

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

4. A compound according to claim 3 of formula II'



II'

wherein R1 and R2 are as defined above for formula I;

R3' is

A) optionally substituted aryl-C_2-C_8-alkyl;

B) optionally substituted heteroarylmethyl; or

C) benzyl which is substituted at the 2-position by lower alkoxy-, hydroxy-lower alkoxy- or lower alkoxy-lower alkoxy; or

when R1 is 2 substituents one of which is OH, preferably at the 6-position, and the other of which is optionally substituted (lower alkyl or lower alkenyl), preferably at the 5-position, R3' is H or optionally substituted (lower alkyl, aryl, aryl-lower alkyl, arylcycloalkyl, cycloalkyl-lower alkyl or carbonyl lower alkyl);

provided that the compound of formula II' is not {2-[2-(3,5-dimethoxy-phenyl)-2-methyl-propylamino]-4,5-dimethoxy-phenyl}-(4-isopropyl-phenyl)-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-3-ylmethyl)-amino]-phenyl}-methanone, (4-isopropyl-phenyl)-{5-methoxy-2-[(pyridin-2-ylmethyl)-amino]-phenyl}-methanone; {2-[2-(2-hydroxy-ethoxy)-benzylamino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone or {2-[(2,3-dimethoxy-quinoxalin-6-ylmethyl)-amino]-5-prop-2-ynyloxy-phenyl}-(4-isopropyl-phenyl)-methanone;

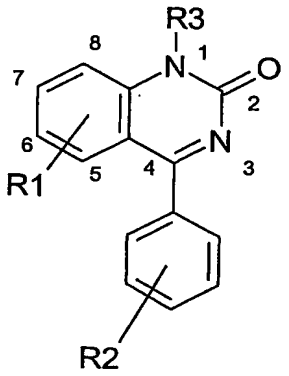
or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof.

5. A method for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable in which an effective amount of a compound of formula I or II as defined above, or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof is administered to a patient in need of such treatment.

6. A pharmaceutical composition for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable comprising a

compound of formula I or II as defined above, or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof, in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

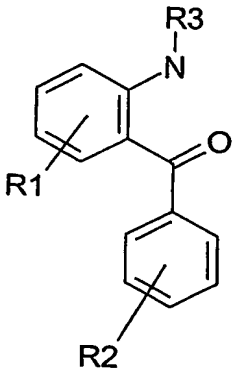
7. A process for the preparation of a compound of formula I



I

wherein the symbols are as defined in claim 1 comprising

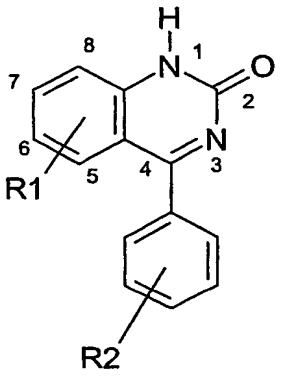
a) cyclising a compound of formula II



II

with a condensation reagent such as chlorosulfonyl isocyanate ($ClSO_2NCO$) or sodium cyanate or sodium thiocyanate; or

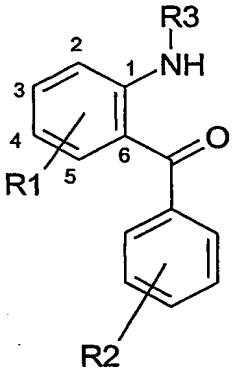
b) for an Agent of the Invention of formula I, in which R3 is optionally substituted aryl-lower alkyl, alkylation of a compound of formula XX



XX

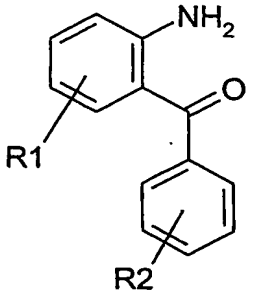
at the 1-position with the corresponding optionally substituted ylhalide;
and thereafter, if required converting the R1, R2 or R3 residues into alternative R1, R2 or R3 residues to give an alternative compound of formula I.

8. A process for the preparation of a compound of formula II



II

wherein R1, R2 and R3 are as defined in claim 1 comprising alkylation of the corresponding aminobenzophenone compound of formula X



X

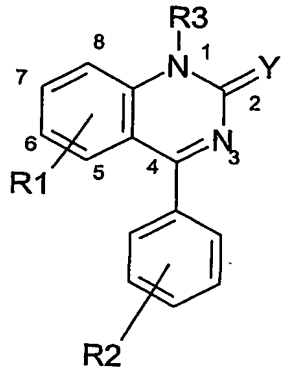
wherein R1 and R2 are as defined in claim 1, and thereafter, if required, converting R1, R2 or R3 residues into alternative R1, R2 or R3 residues to give an alternative compound of formula II.

9. All new methods, compositions and uses as hereinbefore described with particular reference to the Examples.

ABSTRACT

ORGANIC COMPOUNDS

A compound of formula I



I

wherein the symbols are as defined,

or a pharmaceutically-acceptable and –cleavable ester, or acid addition salt thereof, useful for promoting the release of parathyroid hormone, e.g. for preventing or treating bone conditions which are associated with increased calcium depletion or resorption or in which stimulation of bone formation and calcium fixation in the bone is desirable.